Schmidt, M
09/690647



[redacted] ENTERED AT 12:30:41 ON 05 SEP 2001)

```
                E MAPK/CN
L1            3 S E4-E6
                E ERK/CN
L2            3 S E3-E6
                E E10
L3            1 S E10
                E JNK/CN
L4            3 S E3 OR E7-E9
L5           10 S L1 OR L2 OR L3 OR L4
```

FILE [redacted] ENTERED AT 12:32:06 ON 05 SEP 2001

```
L1            3 SEA FILE=REGISTRY ABB=ON  PLU=ON  ("MAPK KINASE"/CN OR
                "MAPK KINASE 3"/CN OR "MAPK KINASE 6"/CN)
L2            3 SEA FILE=REGISTRY ABB=ON  PLU=ON  (ERK/CN OR "ERK 1
                KINASE"/CN OR "ERK 2 KINASE"/CN OR "ERK KINASE"/CN)
L3            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "ERK2 KINASE (CARP)"/CN

L4            3 SEA FILE=REGISTRY ABB=ON  PLU=ON  JNK/CN OR ("JNK
                KINASE"/CN OR "JNK KINASE (CYPRINUS CARPIO ISOENZYME
                A)"/CN OR "JNK KINASE (CYPRINUS CARPIO ISOENZYME B)"/CN)
L5           10 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 OR L2 OR L3 OR L4
L7        11606 SEA FILE=CAPLUS ABB=ON  PLU=ON  (MITOGEN? ACTIV? OR
                SIGNAL REGULAT? OR JUN)(5A)KINASE
L8           13 SEA FILE=CAPLUS ABB=ON  PLU=ON  LIPOLY? AND (L5 OR L7 OR
                MAPK OR JNK OR ERK#)
```

L8 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:265275 CAPLUS
DOCUMENT NUMBER: 134:290417
TITLE: Compounds and methods for modulating non-transcriptional effects of steroid hormones via receptor interaction with phosphatidylinositol-3-kinase
INVENTOR(S): Liao, James K.; Chin, William W.
PATENT ASSIGNEE(S): Brigham & Woman's Hospital, USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001024826 | A2 | 20010412 | WO 2000-US27865 | 20001006 |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,

ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,
BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-158173 P 19991006
US 1999-158525 P 19991008
US 1999-163953 P 19991108
US 1999-163964 P 19991108

AB Methods and compds. are provided for controlling the intracellular and physiol. effects of steroid hormones, including but not limited to estrogen, through modulation of the interaction of such hormone receptors with phosphatidylinositol-3-kinase. Compds. and methods for controlling the activation of endothelial nitric oxide synthase are also disclosed. Related methods for modulation of diseases are also disclosed.

IT **142805-58-1**, MAP kinase kinase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(compds. and methods for modulating non-transcriptional effects of steroid hormones via receptor interaction with phosphatidylinositol kinase)

L8 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:22012 CAPLUS
TITLE: Distinct long-term regulation of glycerol and non-esterified fatty acid release by insulin and TNF-.alpha. in 3T3-L1 adipocytes
AUTHOR(S): Rosenstock, M.; Greenberg, A. S.; Rudich, A.
CORPORATE SOURCE: S. Daniel Abraham Center for Health and Nutrition, Department of Clinical Biochemistry, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
SOURCE: Diabetologia (2001), 44(1), 55-62
CODEN: DBTGAJ; ISSN: 0012-186X
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aims/hypothesis. Adipose tissue **lipolysis** plays a central part in total body fuel metab. Our study was to assess the long-term regulation of glycerol and non-esterified fatty acid (NEFA) release by insulin or TNF-.alpha.. .prgrph.Methods. Fully differentiated 3T3-L1 adipocytes were exposed for up to 22 h to insulin or TNF-.alpha.. .prgrph.Results. Long-term insulin treatment resulted in increased basal glycerol release, reaching sixfold at 22 h with 1 nmol/l insulin. Partial inhibition was obsd.

by pharmacol. inhibiting phosphatidylinositol 3-**kinase** or the **mitogen-activated kinase** ~~**kinase** extracellular~~ **signal-regulated kinase** cascades. This represented 50-60 % of the response induced by 1 nmol/l TNF-.alpha. and approx. 40 % of the glycerol release maximally stimulated by isoproterenol (1 .mu.mol/l, 30 min). The cellular mechanism seemed to be distinct from that of TNF-.alpha.: First, glycerol release in response to long-term insulin was progressive with time and did not display a lag-time characteristic of the effect of TNF-.alpha.. Second, pretreatment and co-treatment of the cells with troglitazone greatly inhibited TNF-.alpha.-induced glycerol release (128.5 .+-. 10.2 to 35.4 .+-. 2.1 nmol/mg protein per h) but not the effect of insulin, which was exaggerated. Third, hormone-sensitive lipase protein content was decreased (45 %) by TNF-.alpha. but not following long-term insulin. Finally, TNF-.alpha. was assocd. with NEFA release to the medium, whereas long-term insulin treatment was not. Moreover, glycerol release during isoproterenol-stimulated **lipolysis** was additive to the effect of long-term insulin, whereas NEFA release was inhibited by nearly 90 %. .prgrph.Conclusions interpretation. Contradictory to its short-term inhibitory effect, long-term insulin stimulates glycerol release with concomitant stimulation of NEFA re-esterification. [Diabetologia (2001) 44: 55-62].

REFERENCE COUNT: 54

REFERENCE(S):
(1) Anthonsen, M; J Biol Chem 1998, V273, P215 CAPLUS
(4) Boden, G; Diabetes 1997, V46, P3 CAPLUS
(5) Botion, L; Diabetes 1999, V48, P1691 CAPLUS
(6) Brasaemle, D; Biochim Biophys Acta 2000, V1483, P251 CAPLUS
(7) Campbell, P; Am J Physiol 1994, V266, PE600 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:535625 CAPLUS
DOCUMENT NUMBER: 133:188255
TITLE: Pancreastatin modulates insulin signaling in rat adipocytes: mechanisms of cross-talk
AUTHOR(S): Gonzalez-Yanes, Carmen; Sanchez-Margalet, Victor
CORPORATE SOURCE: Department of Medical Biochemistry and Molecular Biology, School of Medicine, Investigation Unit, Virgen Macarena University Hospital, University of Seville, Seville, 41009, Spain
SOURCE: Diabetes (2000), 49(8), 1288-1294
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Pancreastatin (PST), a chromogranin A-derived peptide, has counterregulatory effects on insulin in the hepatocyte and the adipocyte, suggesting a possible role in insulin resistance. The mechanism of PST action on glucose and lipid metab. is typical of a calcium-mobilizing hormone and involves a receptor Gq/11 protein-phospholipase C (PLC)-.beta. pathway. In the rat adipocyte, PST inhibits insulin-mediated glucose transport, glucose utilization, and lipid synthesis, and it has a **lipolytic** effect but stimulates basal and insulin-stimulated protein synthesis. We have also recently studied the PST receptor-effector system in adipocyte membranes. To further investigate the mechanisms of PST effect on insulin action, we studied the cross-talk of PST with insulin signaling in the rat adipocyte. We found that PST inhibits insulin-stimulated GLUT4 translocation to the membrane, which may explain the reported inhibition of glucose transport. Tyrosine phosphorylation of the activated insulin receptor, insulin receptor substrate (IRS)-1, and p60-70 was also blunted, preventing their assocn. with p85 phosphatidylinositol 3-kinase (PI3K) and their activity. The mechanism of this inhibition involves the activation of the "classical" protein kinase C isoforms and the serine phosphorylation of insulin receptor and IRS-1. On the other hand, PST activates the **mitogen-activated** protein **kinase (MAPK)** signaling module and enhances the effect of insulin. This pathway may account for the described effect of PST on protein synthesis. In conclusion, PST seems to inhibit the insulin-stimulated PI3K pathway in the adipocyte, whereas it activates the **MAPK** pathway. These data provide some clues to the PST cross-talk with insulin signaling that may explain the PST effects on glucose metab. and protein synthesis.

IT **142243-02-5, Mitogen-activated** protein **kinase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(pancreastatin modulation of insulin signaling in rat adipocytes and mechanisms of cross-talk therein)

REFERENCE COUNT: 68

REFERENCE(S):

(1) Abood, M; Biochem Biophys Res Commun 1990, V167, P1079 CAPLUS
(2) Bossenmaier, B; Diabetologia 1997, V40, P863 CAPLUS
(3) Bradford, M; Anal Biochem 1976, V72, P248 CAPLUS
(5) Curry, W; Regul Pept 1990, V30, P207 CAPLUS
(6) Cushman, S; J Biol Chem 1980, V255, P4758 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:396407 CAPLUS
DOCUMENT NUMBER: 133:130088
TITLE: GH induced **lipolysis** stimulation in 3T3-L1 adipocytes stably expressing hGHR: analysis on signaling pathway and activity of 20K hGH
AUTHOR(S): Asada, N.; Takahashi, Y.; Wada, M.; Naito, N.; Uchida, H.; Ikeda, M.; Honjo, M.
CORPORATE SOURCE: Central Research Institute, Life Sciences Laboratory, Pharmaceuticals Group, Mitsui Chemicals, Inc, Chiba, 297-0017, Japan
SOURCE: Mol. Cell. Endocrinol. (2000), 162(1-2), 121-129
CODEN: MCEND6; ISSN: 0303-7207
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have constructed a cell line of 3T3-L1 which can efficiently express human GHR (3T3-L1-hGHR) after differentiation to adipocytes. The expressed hGHR was detected as two bands with approx. mol. sizes of 120K by Western anal. using hGHR specific monoclonal antibody. Max. **lipolytic** activity induced by hGH in the 3T3-L1-hGHR was enhanced 10-fold as compared to that in 3T3-L1, suggesting that expressed hGHR is functionally active. Comparative anal. using bGH and hGH revealed that 70% of **lipolysis** stimulation by 1-10 ng/mL hGH could be attributed to hGHR-mediated response. Analyses on inhibition and phosphorylation of signaling mols. suggested that GH-induced **lipolysis** stimulation is dependent on gene expression and not mediated through PKA-, PKC-, PLA-, PLC-, nor **MAPK** -pathway but possibly through JAK-STATs pathway. Duration of STAT5 activation by hGH continued up to 48 h. The authors also revealed that 22 K hGH isoform, 20K hGH which has been reported as a weaker agonist for GH-induced **lipolysis** stimulation, possesses equipotent activity and shows stronger action in the presence of hGHBP as compared to 22 K hGH. Taken together the authors conclude that the hGH-induced **lipolysis** was not mediated through MAP-, PKA-, PKC-, nor PLA-pathway but might be mediated through STAT pathway and that 20K hGH might show higher **lipolytic** activity than 22 K hGH in adipose tissue that produces a large amt. of GHBP.

IT **142243-02-5**, MAP kinase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(GH induced **lipolysis** stimulation in 3T3-L1 adipocytes stably expressing hGHR and signaling pathway and activity of 20K hGH)

REFERENCE COUNT: 36
REFERENCE(S):
(1) Amit, T; Endocrinology 1992, V131, P1793 CAPLUS
(2) Balhoff, J; Biochem Biophys Res Commun 1998, V247, P894 CAPLUS
(3) Barnard, R; Biochem J 1990, V267, P471 CAPLUS
(6) Campbell, G; J Biol Chem 1993, V268, P7427 CAPLUS
(7) Carter-Su, C; Annu Rev Physiol 1996, V58, P187 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:775962 CAPLUS
DOCUMENT NUMBER: 132:117856
TITLE: Phosphorylation of extracellular **signal-regulated kinases** 1 and 2 in 3T3-L1 adipocytes by stimulation of .beta.3-adrenoceptor
AUTHOR(S): Mizuno, K.; Kanda, Y.; Kuroki, Y.; Tomiyama, K.; Watanabe, Y.
CORPORATE SOURCE: Department of Pharmacology, National Defense Medical College, Tokorozawa, Japan
SOURCE: Eur. J. Pharmacol. (1999), 385(1), 63-69
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent studies have revealed that activated extracellular **signal-regulated kinases** (**ERKs**) 1 and 2 by the stimulation of .beta.3-adrenoceptors played a crit. role in cell survival in brown adipocytes. Phosphorylation of **ERK1**/2 via .beta.3-adrenoceptors and its physiol. and pathol. significance in white adipocyte has remained uncertain despite the increasing significance of functioning white adipocytes. Accordingly, the authors here studied phosphorylation of **ERK1**/2 caused by the stimulation of .beta.3-adrenoceptors in 3T3-L1 adipocytes, and the roles of phosphorylated **ERK1**/2 in **lipolysis**. Phosphorylation of **ERK1**/2 was induced by a selective .beta.3-adrenoceptor agonist, DL-4-[2'-{2-hydroxy-2-(3-chlorophenyl)ethylamino}propyl] phenoxyacetic acid sodium salt sesquihydrate (BRL37344), in 3T3-L1 adipocytes in a time- and dose-dependent manner. The phosphorylation of **ERK1**/2 by BRL37344 was sensitive to the cAMP-dependent protein kinase inhibitor, N-[2-((p-bromocinnamyl)amino)ethyl]-5-isoquinolinesulfonamide (H89). To elucidate the roles of phosphorylated **ERK1**/2 in

**lipolysis**, the effect of a selective inhibitor of **ERK1**/2 phosphorylation, 2'-amino-3'-methoxyflavone (PD98059), was examd. This inhibitor did not alter the **lipolytic** action caused by BRL37344, even at concns. sufficient to block phosphorylation of **ERK1**/2, suggesting that **ERK1**/2 play no role in the **lipolysis** caused by BRL37344 in 3T3-L1 adipocytes.

IT **137632-07-6**, **Erk1** protein **kinase**
**137632-08-7**, **Erk2** protein **kinase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(phosphorylation of extracellular **signal-regulated kinases** 1 and 2 in 3T3-L1 adipocytes by stimulation of .beta.3-adrenoceptor)

REFERENCE COUNT: 45
REFERENCE(S):
(2) Anderson, N; Nature 1990, V343, P651 CAPLUS
(3) Anthonsen, M; J Biol Chem 1998, V273, P215 CAPLUS
(4) Antras, J; Mol Cell Endocrinol 1991, V82, P183 CAPLUS
(5) Arch, J; Nature 1984, V309, P163 CAPLUS
(6) Boss, O; Biochem Biophys Res Commun 1999, V261, P870 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:742186 CAPLUS
DOCUMENT NUMBER: 132:45408
TITLE: Activation of epithelial growth factor receptor pathway by unsaturated fatty acids
AUTHOR(S): Vacaresse, Nathalie; Lajoie-Mazenc, Isabelle; Auge, Nathalie; Suc, Isabelle; Frisach, Marie-Francoise; Salvayre, Robert; Negre-Salvayre, Anne
CORPORATE SOURCE: INSERM U-466 and Department of Biochemistry, IFR-31, CHU Rangueil, Toulouse, Fr.
SOURCE: Circ. Res. (1999), 85(10), 892-899
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nonesterified fatty acids (NEFAs) are acutely liberated during **lipolysis** and are chronically elevated in pathol. conditions, such as insulin resistance, hypertension, and obesity, which are known risk factors for atherosclerosis. The purpose of this study was to investigate the effect and mechanism of action of NEFAs on the epithelial growth factor (EGF) receptor (EGFR). In the ECV-304 endothelial cell line, unsatd. fatty acids triggered a time-

and dose-dependent tyrosine phosphorylation of EGFR (polyunsatd. fatty acids [PUFAs] were the most active), whereas satd. FAs were inactive. Although less potent than PUFAs, oleic acid (OA) was used because it is prominent in the South European diet and is only slightly oxidizable (thus excluding oxidn. derivs.). EGFR is activated by OA independent of any autocrine secretion of EGF or other related mediators. OA-induced EGFR autophosphorylation triggered EGFR signaling pathway activation (as assessed through coimmunopptn. of SH2 proteins such as SHC, GRB2, and SHP-2) and subsequent p42/p44 **mitogen-activated** protein **kinase** (as shown by the use of EGFR- deficient B82L and EGFR-transduced B82LK+ cell lines). OA induced in vitro both autophosphorylation and activation of intrinsic tyrosine kinase of immunopurified EGFR, thus suggesting that EGFR is a primary target of OA. EGFR was also activated by mild surfactants, Tween-20 and Triton X-100, both in vitro (on immunopurified EGFR) and in intact living cells, thus indicating that EGFR is sensitive to amphiphilic mols. These data suggest that EGFR is activated by OA and PUFAs, acts as a sensor for unsatd. fatty acids (and amphiphilic mols.), and is a potential transducer by which diet compn. may influence vascular wall biol.

IT **137632-07-6**, p44 **Mitogen-activated** protein **kinase** **137632-08-7**, p42 **Mitogen -activated** protein **kinase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(activation of epithelial growth factor receptor pathway by unsatd. fatty acids in human endothelial ECV-304 cells)

REFERENCE COUNT: 46
REFERENCE(S):
(1) Auge, N; J Biol Chem 1998, V273, P12893 CAPLUS
(2) Bae, Y; J Biol Chem 1997, V272, P217 CAPLUS
(3) Bandyopadhyay, G; Prostaglandins Leukot Essent Fatty Acids 1993, V48, P71 CAPLUS
(5) Boden, G; Diabetes 1997, V46, P3 CAPLUS
(6) Brunet, A; Essays Biochem 1997, V32, P1 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:690961 CAPLUS
DOCUMENT NUMBER: 131:281581
TITLE: Methods using a modulator of a **MAPK/ERK, JNK**, or p38 signal transduction pathway for treating and preventing insulin resistance and related disorders
INVENTOR(S): Greenberg, Andrew S.
PATENT ASSIGNEE(S): Trustees of Tufts College, USA

SOURCE: PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9953927 | A1 | 19991028 | WO 1999-US8364 | 19990416 |
| W: JP, US | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| EP 1071429 | A1 | 20010131 | EP 1999-917572 | 19990416 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |

PRIORITY APPLN. INFO.: US 1998-82152 P 19980417
US 1998-82741 P 19980423
WO 1999-US8364 W 19990416

AB The invention provides methods, therapeutics, and kits for treating and preventing diseases or conditions assocd. with excessive **lipolysis**, in particular TNF-.alpha. induced **lipolysis**, and/or excessive free fatty acid levels. Exemplary conditions include insulin-resistance, diabetes (in particular, non-insulin-dependent diabetes mellitus), obesity, glucose intolerance, hyperinsulinemia, polycystic ovary syndrome, and coronary artery disease. In a preferred embodiment, the method includes administering to a subject in need a pharmaceutically effective amt. of an inhibitor of the **JNK** signal transduction pathway and/or an inhibitor of the **MAPK/ERK** signal transduction pathway and/or a stimulator of the p38 signal transduction pathway.

IT **137632-07-6**, **ERK1** kinase **137632-08-7**, **ERK2** kinase **142243-02-5**, MAP kinase **142805-58-1**, MAP kinase kinase **155215-87-5**, **JNK** kinase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**MAPK/ERK**, **JNK**, or p38 signal transduction pathway modulator for treatment of disorders assocd. with TNF-.alpha.-induced **lipolysis**)

REFERENCE COUNT: 13
REFERENCE(S):
(2) Font De Mora, J; Mol Cell Biol 1997, V17(10), P6068 CAPLUS
(4) Kliewer; Cell 1995, V83, P813 CAPLUS
(5) Pearson; Biochem Biophys Res Commun 1996, V229, P752 CAPLUS
(6) Sale; EMBO J 1995, V14(4) CAPLUS

Searcher : Shears 308-4994

(7) Schoenhoefer, P; Biochem Pharmacol 1973, V22, P629 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:400600 CAPLUS
DOCUMENT NUMBER: 129:118040
TITLE: Growth hormone and prolactin stimulate tyrosine phosphorylation of insulin receptor substrate-1, -2, and -3, their association with p85 phosphatidylinositol 3-kinase (PI3-kinase), and concomitantly PI3-kinase activation via JAK2 kinase
AUTHOR(S): Yamauchi, Toshimasa; Yasushi, Kaburagi; Ueki, Kohjiro; Tsuji, Yuki; Stark, George R.; Kerr, Ian M.; Tsushima, Toshio; Akanuma, Yasuo; Komuro, Issei; Tobe, Kazuyuki; Yazaki, Yoshio; Kadowaki, Takashi
CORPORATE SOURCE: Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo, 113, Japan
SOURCE: J. Biol. Chem. (1998), 273(25), 15719-15726
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Growth hormone (GH) and prolactin (PRL) binding to their receptors, which belong to the cytokine receptor superfamily, activate Janus kinase (JAK) 2 tyrosine kinase, thereby leading to their biol. actions. The authors recently showed that GH mainly stimulated tyrosine phosphorylation of epidermal growth factor receptor and its assocn. with Grb2, and concomitantly stimulated **mitogen-activated** protein **kinase** activity in liver, a major target tissue. Using specific antibodies, the authors now show that GH was also able to induce tyrosine phosphorylation of insulin receptor substrate (IRS)-1/IRS-2 in liver. In addn., the major tyrosine-phosphorylated protein in anti-p85 phosphatidylinositol 3-kinase (PI3-kinase) immunoppt. from liver of wild-type mice was IRS-1, and IRS-2 in IRS-1 deficient mice, but not epidermal growth factor receptor. These data suggest that tyrosine phosphorylation of IRS-1 may be a major mechanism for GH-induced PI3-kinase activation in physiol. target organ of GH, the liver. The authors also show that PRL was able to induce tyrosine phosphorylation of both IRS-1 and IRS-2 in COS cells transiently transfected with PRLR and in CHO-PRLR cells. Moreover, the authors show that tyrosine phosphorylation of IRS-3 was induced by both GH and PRL in COS cells transiently transfected with IRS-3 and their

cognate receptors. By using the JAK2-deficient cell lines or by expressing a dominant neg. JAK2 mutant, the authors show that JAK2 is required for the GH- and PRL-dependent tyrosine phosphorylation of IRS-1, -2, and -3. Finally, a specific PI3-kinase inhibitor, wortmannin, completely blocked the anti-lipolytic effect of GH in 3T3 L1 adipocytes. Taken together, the role of IRS-1, -2, and -3 in GH and PRL signalings appears to be phosphorylated by JAK2, thereby providing docking sites for p85 PI3-kinase and activating PI3-kinase and its downstream biol. effects.

L8 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:195819 CAPLUS
DOCUMENT NUMBER: 129:743
TITLE: Lipid metabolism in fibroblast growth factor-stimulated L6 myoblasts: a receptor mutation (Y766F) abrogates phospholipase D and diacylglycerol kinase activities
AUTHOR(S): van Dijk, Marc C. M.; van Blitterswijk, Wim J.
CORPORATE SOURCE: Division of Cellular Biochemistry, The Netherlands Cancer Institute, Amsterdam, 1066 CX, Neth.
SOURCE: Biochim. Biophys. Acta (1998), 1391(2), 273-279
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phosphatidylcholine (PC) hydrolysis induced by basic fibroblast growth factor (bFGF) was studied in rat L6 myoblasts expressing the wild-type FGF receptor-1 (FGFR-1) or a mutant (Y766F) that is incapable of activating phospholipase C-.gamma. (PLC.gamma.). Stimulation of FGFR-1 activated phospholipase D (PLD) rapidly and transiently, but did not induce PC-specific PLC activity. Downregulation of protein kinase C blocked bFGF-induced PLD activation but not phosphatidic acid formation by diacylglycerol (DG) kinase. Only phosphoinositide (PI)-derived DG, not PC-derived DG, appeared to be a substrate for DG kinase. Stimulation of FGFR-1(Y766F) did not activate PLD or DG kinase, both of which apparently require initial PLC.gamma. activation. The Y766F mutation reduced **mitogen-activated** protein **kinase** activation but not cell proliferation. We conclude that both PI turnover and PC hydrolysis are dispensable for bFGF-induced mitogenesis.
IT **142243-02-5, Mitogen-activated** protein **kinase**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(lipid metab. in fibroblast growth factor-stimulated L6 myoblasts in relation to phospholipases and the MAP kinase signaling

pathway)

L8 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:164954 CAPLUS
DOCUMENT NUMBER: 128:304236
TITLE: **Mitogen-activated** protein **kinase** and p70 ribosomal protein S6 kinase are not involved in the insulin-dependent stimulation of cAMP phosphodiesterase kinase in rat adipocytes
AUTHOR(S): Onuma, Hiroshi; Makino, Hideichi; Osawa, Haruhiko; Suzuki, Yoshifumi; Taira, Masato; Kanatsuka, Azuma; Saito, Yasushi
CORPORATE SOURCE: Department of Laboratory Medicine, Ehime University, School of Medicine, Ehime, 791-02, Japan
SOURCE: Biochim. Biophys. Acta (1998), 1402(2), 197-208
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To elucidate the mechanism of anti-**lipolytic** action of insulin in rat epididymal adipocytes, the authors explored the potential mechanism that might be involved in the hormone-dependent stimulation of cAMP phosphodiesterase (PDE) kinase. PDE kinase was assayed in a cell-free system. Both wortmannin and LY294002, highly specific inhibitors of phosphatidylinositol 3-kinase, almost completely blocked the hormonal effect not only on PDE **kinase** but also on **mitogen-activated** protein (MAP) **kinase**. Neither PD98059, a specific inhibitor of MAP kinase, nor rapamycin, a potent inhibitor of insulin-dependent stimulation of p70 ribosomal protein S6 kinase (p70S6K), had inhibitory effect on that of PDE kinase. These results are consistent with the view that (i) insulin-activated PDE kinase as well as MAP kinase and p70S6K are localized downstream of phosphatidylinositol 3-kinase, (ii) PDE kinase is distinct from either MAP kinase or p70S6K and (iii) PDE kinase does not exist downstream of either MAP kinase or p70S6K. It is suggested that PDE kinase and MAP kinase or p70S6K may be localized in sep. branches of the cascade of insulin action. The branching point of the cascade could be either at or below the level of phosphatidylinositol 3-kinase.

IT **142243-02-5**, **Mitogen-activated** protein **kinase**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(MAP **kinase** and p70 ribosomal protein S6 kinase independence from insulin-dependent stimulation of cAMP

ISSN: 0002-9149.
DOCUMENT TYPE: General Review; Article
LANGUAGE: English

AB The metabolic effects of insulin are initiated by the binding of insulin to the extracellular domain of the insulin receptor within the plasma membrane of muscle and adipose and liver cells. The subsequent activation of the intracellular tyrosine protein kinase activity of the receptor leads to autophosphorylation of the receptor as well as phosphorylation of a number of intracellular proteins. This gives rise to the activation of Ras and phosphatidylinositol 3-kinase and hence to the activation of a number of serine/threonine protein kinases. Many of these kinases appear to be arranged in cascades, including a cascade that results in the activation of **mitogen-activated** protein **kinase** and another that may result in the activation of protein kinase B, leading to the inhibition of glycogen synthase kinase-3 and the activation of the 70 kiloDalton ribosomal S6 protein kinase (p70 S6 kinase). We have explored the role of these early events in the stimulation of glycogen, fatty acid, and protein synthesis by insulin in rat epididymal fat cells. Comparisons have been made between the metabolic effects of insulin and those of epidermal growth factor, since these 2 agents have contrasting effects on p70 S6 **kinase** and **mitogen-activated** protein **kinase**. The effects of wortmannin (which inhibits phosphatidylinositol 3-kinase), and rapamycin (which blocks the activation of p70 S6 kinase) have also been studied. These and other studies indicate that the **mitogen-activated** protein **kinase** cascade is probably not important in the acute metabolic effects Of insulin, but may have a role in the regulation of gene transcription and hence the more long-term effects of insulin. The short-term metabolic effects of insulin appear to involve at least 3 distinct signaling pathways: (1) those leading to increases in glucose transport and the activation of glycogen synthase, acetyl-CoA carboxylase, eukaryotic initiation Factor-2B, and phosphodiesterase, which may involve phosphatidylinositol 3-kinase and protein kinase B; (2) those leading to some of the effects of insulin on protein synthesis (formation of eukaryotic initiation factor-4F complex, S6 phosphorylation, and activation of eukaryotic elongation factor-2), which may involve phosphatidylinositol 3-kinase and p70 S6 kinase; and finally, (3) that leading to the activation of pyruvate dehydrogenase, which is unique in apparently not requiring activation of phosphatidylinositol 3-kinase.

L10 ANSWER 24 OF 24 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95185330 EMBASE
DOCUMENT NUMBER: 1995185330
TITLE: Phosphatidylinositol 3-kinase signals activation of

p70 S6 kinase in situ through site-specific p70 phosphorylation.

AUTHOR: Weng Q.-P.; Andrabi K.; Klippel A.; Kozlowski M.T.; Williams L.T.; Avruch J.

CORPORATE SOURCE: Diabetes Research Laboratory, Massachusetts General Hospital, 149 13th Street,Charlestown, MA 02129, United States

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1995) 92/12 (5744-5748).
ISSN: 0027-8424 CODEN: PNASA6

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 021 Developmental Biology and Teratology
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The p70 S6 kinase is activated by insulin and mitogens through multisite phosphorylation of the enzyme. One set of activating phosphorylations occurs in a putative autoinhibitory domain in the noncatalytic carboxyl-terminal tail. Deletion of this tail yields a variant (p70.DELTA.CT104) that nevertheless continues to be mitogen regulated. Coexpression with a recombinant constitutively active phosphatidylinositol (PI) 3-kinase (EC 2.7.1.137) gives substantial activation of both full-length p70 and p70.DELTA.CT104 but not Rsk. Activation of p70.DELTA.CT104 by PI 3-kinase and inhibition by wortmannin are each accompanied by parallel and selective changes in the phosphorylation of p70 Thr-252. A Thr or Ser at this site, in subdomain VIII of the catalytic domain just amino-terminal to the APE motif, is necessary for p70 40S kinase activity. The inactive ATP-binding site mutant K123M p70.DELTA.CT104 undergoes phosphorylation of Thr-252 in situ but does not undergo direct phosphorylation by the active PI 3-kinase in vitro. PI 3-kinase provides a signal necessary for the **mitogen activation** of the p70 S6 **kinase**, which directs the site-specific phosphorylation of Thr-252 in the p70 catalytic domain, through a distinctive signal transduction pathway.

[redacted] ENTERED AT 12:40:02 ON 05 SEP 2001
E RIBOZYME/CN
L11 823 SEA ABB=ON PLU=ON RIBOZYME ?/CN
E RIBOZYMES/CN
E SODIUM SALICYLATE/CN 5
L12 1 SEA ABB=ON PLU=ON ("SODIUM SALICYLATE"/CN OR "SODIUM SALICYLATE (NAO3C7H5)"/CN)
L13 824 SEA ABB=ON PLU=ON L11 OR L12

FILE 'CAPLUS' ENTERED AT 12:40:51 ON 05 SEP 2001

L14 11962 SEA ABB=ON PLU=ON L13 OR (NA OR SODIUM)(W)SALICYLATE OR RIBOZYME OR (TRIPLE# OR ANTISENS? OR ANTI SENS?)(W)MOL ECUL?
L15 15 SEA ABB=ON PLU=ON L14 AND LIPOLY?

L16 14 L15 NOT L8

L16 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1981:422486 CAPLUS
DOCUMENT NUMBER: 95:22486
TITLE: Importance of ischemia-induced myocardial **lipolysis** in dogs
AUTHOR(S): Vik-Mo, H.; Mioes, O. D.; Riemersma, R. A.; Oliver, M. F.
CORPORATE SOURCE: Inst. Med. Biol., Univ. Tromso, Tromso, Norway
SOURCE: Adv. Physiol. Sci., Proc. Int. Congr., 28th (1981), Meeting Date 1980, Volume 8, Issue Cardiovasc. Physiol.: Heart, Peripher. Circ. Methodol., 121-8. Editor(s): Kovach, A. G. B.; Monos, E.; Rubanyi, G. Akad. Kiado: Budapest, Hung.
CODEN: 45TGAW
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Induction of myocardial ischemia induced glycerol release from the ischemic area; no glycerol uptake or release was obsd. in or from the nonischemic area. During isoprenaline infusion no ischemia-induced enhancement of myocardial **lipolysis** was found. Free fatty acids (FFA) were extd. from plasma in the ischemic area. A decrease of plasma FFA by the antilipolytic agents nicotinic acid or **Na salicylate** decreased the FFA extn. by the ischemic myocardium in the basal state or during isoprenaline infusion. Ischemia increased the extn. of glucose and O and the release of lactate by the myocardium in the basal state or during isoprenaline infusion.

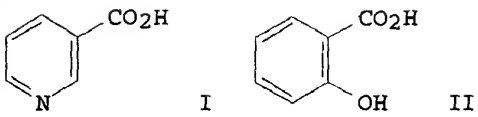
L16 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1980:18004 CAPLUS
DOCUMENT NUMBER: 92:18004
TITLE: High purity xanthine oxidase from bovine milk
INVENTOR(S): Zikakis, John P.
PATENT ASSIGNEE(S): University of Delaware, USA
SOURCE: U.S., 5 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 4172763 | A | 19791030 | US 1977-806736 | 19770615 |
| US 4246341 | A | 19810120 | US 1979-14337 | 19790223 |
| US 4238566 | A | 19801209 | US 1980-114047 | 19800121 |
| PRIORITY APPLN. INFO.: | | | US 1977-806736 | 19770615 |
| | | | US 1979-14338 | 19790223 |

AB A method is described for the isolation and purifn. of xanthine oxidase from raw whole milk without the use of proteolytic or **lipolytic** enzymes or org. solvents. Thus, **Na salicylate**, EDTA, and cysteine-HCl are added to raw milk as enzyme protectors and the mixt. is dild. 1:1 with K2HPO4 buffer and incubated at 40-45.degree. for 2 h under continuous stirring. After 105 min of incubation, 1% by vol. of Triton X-100 is added and the mixt. is incubated for 15 min. The mixt. is then cooled to 4.degree. and all subsequent steps are carried out at this temp. A 2-step fractionation of proteins with (NH4)2SO4 gives a red-brown ppt. which is dissolved in a minimal vol. of 0.1M Tris/CaCl2, pH 7.0, and stored at -20.degree. for 0.5 to 7 days to ppt. caseins. After thawing, centrifugation, and concn. on a XM50 microfilter, the isolated enzyme is purified by column chromatog. steps on Sephadex G-75, Sephacryl S-200, Sepharose 6B, and Sephadex G-75. Final purifn. is achieved by ion-exchange chromatog. on DEAE-Sephadex A-50 with a continuous linear salt gradient of 0.005-0.1M Na pyrophosphate. Purified xanthine oxidase has an av. E280/E450 ratio of 4.1 and shows 1 sym. peak on gel chromatog. and a single band on polyacrylamide disc gel electrophoresis. The av. yield is .apprx.21%.

L16 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2001 ACS

| | |
|---|---|
| ACCESSION NUMBER: | 1980:15570 CAPLUS |
| DOCUMENT NUMBER: | 92:15570 |
| TITLE: | Effect of myocardial ischemia and antilipolytic agents on **lipolysis** and fatty acid metabolism in the in situ dog heart |
| AUTHOR(S): | Vik-Mo, Harald; Riemersma, Rudolph A.; Mjoes, Ole D.; Oliver, Michael F. |
| CORPORATE SOURCE: | Inst. Med. Biol., Univ. Tromso, Tromso, Norway |
| SOURCE: | Scand. J. Clin. Lab. Invest. (1979), 39(6), 559-68<br>CODEN: SJCLAY; ISSN: 0036-5513 |
| DOCUMENT TYPE: | Journal |
| LANGUAGE: | English |
| GI | |

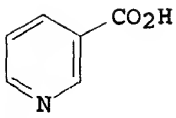


I II

AB Myocardial metab. was studied in open-chest dogs before and during induction of myocardial ischemia by coronary artery occlusion. In the basal state, induction of myocardial ischemia stimulated myocardial **lipolysis** as shown by release of glycerol from the ischemic zone. During isoprenaline infusion, free fatty acids (FFA) extn. across the ischemic myocardium was substantially increased, but no glycerol release occurred. Pretreatment with nicotinic acid (I) [59-67-6] or **Na salicylate** (II Na salt) [**54-21-7**] markedly depressed FFA extn. across ischemic myocardium, both during basal and isoprenaline stimulated **lipolysis** and I most likely inhibited **lipolysis** in the ischemic zone. Thus, reduced severity of acute ischemic injury by antilipolytic treatment might be due to a combination of inhibited myocardial **lipolysis** and reduced FFA extn.

IT **54-21-7**
RL: BIOL (Biological study)
(fatty acid metab. and **lipolysis** response to, in heart during ischemia)

L16 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1978:523093 CAPLUS
DOCUMENT NUMBER: 89:123093
TITLE: Mechanisms for inhibition of free fatty acid mobilization by nicotinic acid and **sodium salicylate** in canine subcutaneous adipose tissue in situ
AUTHOR(S): Vik-Mo, Harald; Mjoes, Ole D.
CORPORATE SOURCE: Inst. Med. Biol., Univ. Tromsoe, Tromsoe, Norway
SOURCE: Scand. J. Clin. Lab. Invest. (1978), 38(3), 209-16
CODEN: SJCLAY; ISSN: 0036-5513
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Mechanisms for reduced free fatty acid (FFA) mobilization elicited by nicotinic acid (I) [59-67-6] and **sodium salicylate** [**54-21-7**] were studied in canine adipose tissue in situ. Both drugs inhibited adipose tissue **lipolysis** as evidenced by reduced release of glycerol. In addn., although the total amt. of FFA re-esterified was not significantly changed, the amt. of FFA re-esterified relative to the amt. of FFA liberated intracellularly was significantly increased by both drugs. These effects were most pronounced during isoprenaline-stimulated **lipolysis**. Thus, I and salicylate reduced mobilization of FFA from canine adipose tissue through a combined effect on re-esterification and **lipolysis**.

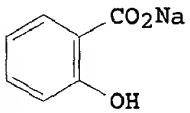
IT **54-21-7**
RL: BIOL (Biological study)
(fatty acid metab. response to, in adipose tissue)

L16 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1978:453430 CAPLUS
DOCUMENT NUMBER: 89:53430
TITLE: Effects of **sodium salicylate** on plasma insulin concentration and fatty acid turnover in dogs
AUTHOR(S): Vik-Mo, Harald; Hove, Knut; Mjoes, Ole D.
CORPORATE SOURCE: Inst. Med. Biol., Univ. Tromsoe, Tromsoe, Norway
SOURCE: Acta Physiol. Scand. (1978), 103(2), 113-19
CODEN: APSCAX; ISSN: 0001-6772
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of i.v. **Na salicylate** [**54-21-7**] administration on plasma concns. of insulin [9004-10-8], free fatty acids (FFA), and glucose [50-99-7] were studied in intact, anesthetized dogs both during basal and isoprenaline [7683-59-2] stimulated **lipolysis**. In both situations **Na salicylate** reduced the plasma concns. of insulin. The redn. was assocd. with decreased plasma FFA concns. and FFA turnover rate, while plasma glucose concns. remained unaltered. The reduced plasma insulin concns. effected by **Na salicylate** is most likely secondary to the concomitant fall in plasma FFA concns. due to inhibition of FFA mobilization from adipose tissue.

IT **54-21-7**
RL: BIOL (Biological study)
(fatty acid metab. and plasma glucose and insulin response to)

L16 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1977:495695 CAPLUS
DOCUMENT NUMBER: 87:95695
TITLE: Myocardial metabolism and performance during **sodium salicylate** infusion in dogs
AUTHOR(S): Vik-Mo, H.; Mjos, O. D.
CORPORATE SOURCE: Inst. Med. Biol., Univ. Tromsoe, Tromsoe, Norway
SOURCE: Scand. J. Clin. Lab. Invest. (1976), 36(8), 763-9
CODEN: SJCLAY
DOCUMENT TYPE: Journal
LANGUAGE: English
GI




I

AB The effect of **sodium salicylate** (I) [**54-21-7**] on net myocardial free fatty acid (FFA) uptake, myocardial O consumption (MVO2), and the mech. activity of the heart was studied in 8 intact, anesthetized dogs. I was given i.v. under basal conditions and during isoproterenol-stimulated **lipolysis**. Under basal conditions, I reduced arterial FFA concn., but did not influence net myocardial uptake of FFA, and MVO2 was unchanged. During isoproterenol infusion I reduced arterial FFA concn. by 28% reduced net myocardial uptake of FFA from 44.5 to 22.3 .mu.mol/min. 100 g tissue and MVO2 from 20.3 to 16.0 ml/min. 100 g tissue. The redn. in MVO2 could not be explained by reduced mech. activity of the heart. Most probably the mechanism for the redn. in MVO2 effected by I during isoproterenol infusion was mediated by reduced myocardial FFA consumption.
IT **54-21-7**
RL: BIOL (Biological study)
(heart respiration and lipid metab. response to)

L16 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1977:183201 CAPLUS
DOCUMENT NUMBER: 86:183201

TITLE: Studies on antilipolytic activity of antipyretics. Part I. Influence of **sodium salicylate**, phenazone, aminophenazone, acetylsalicylic acid, and acetophenidin on **lipolysis** in fever induced by E. coli pyrogen

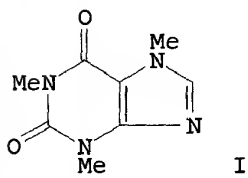
AUTHOR(S): Matuszek, Maria
CORPORATE SOURCE: Inst. Pathol., Med. Acad., Gdansk, Pol.
SOURCE: Pol. J. Pharmacol. Pharm. (1976), 28(5), 429-35
CODEN: PJPPAA
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fever and **lipolysis** induced by pyrogen (1 .mu.g/kg, i.v.) in rabbits were inhibited by orally administered **Na salicylate** [54-21-7], acetylsalicylic acid [50-78-2], phenazone [60-80-0], aminophenazone [58-15-1], or acetophenidin [62-44-2], all at a dose of 170 mg/kg.
IT **54-21-7**
RL: BIOL (Biological study)
(**lipolysis** response to, in fever)

L16 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1977:150400 CAPLUS
DOCUMENT NUMBER: 86:150400
TITLE: Studies on antilipolytic activity of antipyretics. Part II. Influence of **sodium salicylate**, and acetophenetidin on aminophenazone, and acetophenetidin on **lipolysis** stimulated by noradrenaline and aminophylline in vitro

AUTHOR(S): Matuszek, Maria
CORPORATE SOURCE: Inst. Pathol., Med. Acad., Gdansk, Pol.
SOURCE: Pol. J. Pharmacol. Pharm. (1976), 28(5), 437-42
CODEN: PJPPAA
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Lipolysis** of rat epididymal fat tissue was stimulated by noradrenaline (NA) [51-41-2] and aminophyline [317-34-0]. **Sodium salicylate** [**54-21-7**] inhibited the **lipolysis** stimulated by NA, but not by aminophylline. Aminophenazone [58-15-1] and acetophenetidin [62-44-2] inhibited **lipolysis** stimulated either by NA or by aminophylline. The antipyretics inhibited stimulated **lipolysis** in a noncompetitive manner.
IT **54-21-7**
RL: BIOL (Biological study)
(**lipolysis** inhibition by)

Searcher : Shears 308-4994

L16 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1977:37711 CAPLUS
DOCUMENT NUMBER: 86:37711
TITLE: Role of caffeine-stimulated **lipolysis** in the context of pathological pregnancy
AUTHOR(S): Riemer, W. D.; Prott, V.; Franke, G.
CORPORATE SOURCE: Univ.-Frauenklin., Greifswald, E. Ger.
SOURCE: Zentralbl. Gynaekol. (1976), 98(18), 1137-43
CODEN: ZEGYAX
DOCUMENT TYPE: Journal
LANGUAGE: German
GI



I

AB Injection of caffeine **Na salicylate** (I **Na salicylate**) [8002-85-5] (3 mg/kg, i.v.) into healthy women in the 1st trimester of pregnancy increased blood glycerol and free fatty acid concns., indicative of a stimulator of **lipolysis**. Such enhanced **lipolysis** might be of significance in the pathol. of pregnancy, and possible mechanisms are discussed whereby it could induce premature labor. To prevent a possible cause of abortion or miscarriage, a considerable restriction of coffee intake throughout pregnancy is recommended.

L16 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1976:12628 CAPLUS
DOCUMENT NUMBER: 84:12628
TITLE: Effects of caffeine on blood-glucose, IRI [immunoreactive insulin] concentrations, and **lipolysis** parameters in man
AUTHOR(S): Ratzmann, Klaus P.; Riemer, D.; Maennchen, E.
CORPORATE SOURCE: Med. Klin. Poliklin., Ernst-Moritz-Arndt-Univ., Greifswald, E. Ger.
SOURCE: Dtsch. Z. Verdau.- Stoffwechselkr. (1975), 35(3), 129-33
CODEN: DZVSAT
DOCUMENT TYPE: Journal

LANGUAGE: German

AB Caffeine-**Na salicylate** mixt. [8002-85-5] (3 mg/kg i.v.) did not affect the blood sugar and immunoreactive insulin [9004-10-8] concns. in peripheral venous blood of healthy subjects, but stimulated **lipolysis**, as indicated by an increase blood fatty acid and glycerol levels. The significance of coffee drinking in the pathogenesis of arteriosclerosis was discussed.

L16 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1973:427124 CAPLUS

DOCUMENT NUMBER: 79:27124

TITLE: Effects of **sodium salicylate** and acetylsalicyclic acid on the **lipolytic** system of fat cells

AUTHOR(S): Schoenhoefer, Peter S.; Sohn, Joachim; Peters, Hans D.; Dinnendahl, Volker

CORPORATE SOURCE: Inst. Pharmacol., Univ. Bonn, Bonn, Ger.

SOURCE: Biochem. Pharmacol. (1973), 22(5), 629-37
CODEN: BCPCA6

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Na salicylate** (I) [**54-21-7**] and acetylsalicylic acid (II) [50-78-2] (each at 10-4-10-2M) caused a dose-dependent inhibition of the **lipolysis** which occurs in isolated fat cells on stimulation by 10-6M norepinephrine [51-41-2] or 3 .tim. 10-3M dibutyryl cyclic AMP [362-74-3]. I decreased cellular ATP [56-65-5] levels in the same dose range in which **lipolysis** inhibition occurred, while II had no effect on ATP. Both I and II decreased cyclic AMP [60-92-4] accumulation and inhibited phosphodiesterase [9025-82-5]. Both I and II decreased the binding of cyclic AMP to cyclic AMP-dependent protein kinase [9026-43-1], I being more effective than than II. This decrease in binding may be essential for the antilipolytic effect of both salicylates.

IT **54-21-7**
RL: BIOL (Biological study)
(**lipolysis** inhibition from)

L16 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1971:74796 CAPLUS

DOCUMENT NUMBER: 74:74796

TITLE: Influence of pyrogen (LPS), dinitrophenol (DNP), some antipyretic drugs, and prostaglandin E1 (PGE1), on plasma free fatty acids (FFA) and blood glucose in rabbits

AUTHOR(S): Korolkiewicz, Zbigniew; Matuszek, Maria; Pocwiardowska, Eugenia

CORPORATE SOURCE: Dep. Pharmacol., Med. Acad., Gdansk, Pol.
SOURCE: Diss. Pharm. Pharmacol. (1970), 22(5), 257-61
CODEN: DPHFAK
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB 2,4-Dinitrophenol (I) (20 mg/kg) and Escherichia coli lipopolysaccharides (LPS) (0.15 .gamma./kg) given i.v. to rabbits increased plasma free fatty acids; this effect was inhibited by pretreatment with **Na salicylate** (II) (171 mg/kg orally) and prostaglandin E1 (6 .gamma./kg). Increases in plasma free fatty acids by theophylline (III) (100 mg/kg i.p.) were also inhibited by pretreatment with II and the prostaglandin. III-induced **lipolysis** was also inhibited by acetylsalicylic acid (215 mg/kg) and acetophenetidin (50 mg/kg). Thus, the antilipolytic effects of II acetylsalicylic acid, and acetophenetidin seem to play an important part in the mechanism of antipyretic action of these drugs. Neither pyrogens and III nor the antipyretics affected blood glucose levels. Oxidative phosphorylation in liver mitochondria was not important in exptl. hyperthermia and in the antipyretic action of II.
IT **54-21-7**
RL: BIOL (Biological study)
(antipyretic action of, fatty acids of blood plasma in relation to)

L16 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1969:459276 CAPLUS
DOCUMENT NUMBER: 71:59276
TITLE: Effect of **sodium salicylate** on induced **lipolysis** in isolated fat cells of the rat
AUTHOR(S): Stone, Daniel Boxall; Brown, Joseph D.; Steele, Ann A.
CORPORATE SOURCE: Univ. Hosp., Iowa City, Iowa, USA
SOURCE: Metab., Clin. Exp. (1969), 18(7), 620-4
CODEN: METAAJ
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Na salicylate** reduced the rate of release of glycerol and fatty acids from fat cells isolated from epidiymal adipose tissue of fasted rats induced by DL-arterenol, glucagon, theophylline, ACTH, dexamethasone plus growth hormone, and dibutyryl cyclic AMP plus theophylline. **Na salicylate** appeared to be a nonspecific inhibitor of **lipolysis** in adipose tissue cells.
IT **54-21-7**
RL: BIOL (Biological study)

Searcher : Shears 308-4994

(pharmaceutical-induced **lipolysis** inhibition by)

L16 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1963:484923 CAPLUS
DOCUMENT NUMBER: 59:84923
ORIGINAL REFERENCE NO.: 59:15785d-e
TITLE: Effect of salicylate on plasma nonesterified fatty acids
AUTHOR(S): Gilgore, Sheldon G.; Drew, Lawrence W.; Rupp, Joseph J.
CORPORATE SOURCE: Jefferson Med. Coll., Philadelphia, PA
SOURCE: Am. J. Med. Sci. (1963), 245, 456-8
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Blood sugar (I) levels and plasma level of nonesterified fatty acids (II) were measured in a control group and in diabetic patients after intravenous infusion of **Na salicylate** (III). No change in I and a rise in II were noted in the control group. A drop in I and a rise in II were noted in diabetic patients. III has an insulinlike action on carbohydrate metabolism, but exerts a **lipolytic** effect on fat metabolism in contrast to an antilipolytic action on fat by insulin.

([redacted]INE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, [redacted]JADIO' ENTERED AT 12:42:52 ON 05 SEP 2001)
L17 37 S L15
L[redacted] 36 S L17 NOT L9
L[redacted] [redacted] DUPLICATES REMOVED)

L19 ANSWER 1 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-007397 [01] WPIDS
DOC. NO. CPI: C2001-001896
TITLE: New autotaxin proteins, useful e.g. for treating diabetes mellitus and obesity, stimulate glucose uptake by cells and inhibit **lipolysis**.
DERWENT CLASS: B04 D16
INVENTOR(S): KELLY, J D
PATENT ASSIGNEE(S): (ZYMO) ZYMOGENETICS INC
COUNTRY COUNT: 91
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2000068386 | A1 | 20001116 | (200101)* | EN | 124 |

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP

Searcher : Shears 308-4994

KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT
RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000048250 A 20001121 (200112)

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 2000068386 A1 | | WO 2000-US12402 | 20000505 |
| AU 2000048250 A | | AU 2000-48250 | 20000505 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 2000048250 A | | Based on | WO 200068386 |

PRIORITY APPLN. INFO: US 1999-306979 19990507
AN 2001-007397 [01] WPIDS
AB WO 200068386 A UPAB: 20001230
NOVELTY - An isolated polypeptide (I) at least 70 % identical to residues 32-858 of an 858 amino acid sequence (S2), fully defined in the specification, that binds specifically to an antibody that binds to (S2), provided that (I) is not an autotaxin (At) from human melanoma (GenBank L35594), human teratocarcinoma (L46720) or rat brain (1083752 or BAA05910), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated polypeptide (Ia) comprising residues 32-858 or 149-158 of (S2) or residues 45-859 of an 859 amino acid sequence (S9), fully defined in the specification;

(2) isolated nucleic acid (II) that

(a) comprises a 2574 base pair sequence (S3), fully defined in the specification; or

(b) hybridizes under stringent conditions to a 2828 base pair sequence (S1), fully defined in the specification, or its complement, provided that it does not encode any of the three At excluded above;

(3) isolated nucleic acid (IIa) that encodes (Ia) and comprises nucleotides 223-2703 of (S1), or 237-2681 of (S9);

(4) vector containing (IIa);

(5) expression vector containing (IIa) plus transcription promoter and terminator;

(6) recombinant host cell containing the vector of (5);

(7) production of autotaxin proteins (At) by culturing the cells of (6), under expression conditions, and recovering the polypeptide;

(8) antibody (Ab), or its fragments, that bind specifically to

(Ia), i.e. to an epitope comprising the defined amino acid regions;

(9) anti-idiotype antibody (AAb), or its fragment, that binds specifically to Ab;

(10) recombinant virus containing the vector of (5), or a similar vector in which (II) can be any sequence encoding At or its analog;

(11) pharmaceutical composition containing the vector of (5), or a similar vector in which (II) can be any sequence encoding At or its analog, the virus of (10) , (Ia) or any At or analog, plus a carrier; and

(12) stimulating cellular glucose uptake by administering At or its analog.

ACTIVITY - Hypoglycemic; antidiabetic; anorectic; antilipemic. No biological data is given.

MECHANISM OF ACTION - Autotaxins (At) increase insulin signaling in adipose tissue by producing substrate for adenosine receptors, resulting in inhibition of **lipolysis**, decreased hepatic gluconeogenesis and serum glucose levels, and increased insulin sensitivity. They also inhibit differentiation of adipocytes. At have type I phosphodiesterase, adenosine-5'-triphosphatase (ATPase) and ATP pyrophosphatase activities.

USE - (I), which are autotaxins (At), and their analogs are used to stimulate glucose uptake by cells, either in culture or in vivo, particularly to reduce serum glucose levels for treatment of non-insulin dependent diabetes in humans, or generally any condition associated with elevated serum levels of glucose, lipid or free fatty acid (e.g. obesity or dyslipidemia). (I), and their anti-idiotypic antibodies, can be used to identify and isolate At receptors and to raise specific antibodies (Ab) for in vivo or in vitro detection of At, also therapeutically to inhibit At overexpression and to screen for At-encoding sequences. Nucleic acids that encode (I) are used for recombinant production of proteins (including expression from gene therapy vectors), as antisense sequences, **ribozymes** etc. for inhibiting At expression, as probes and primers for detecting or localizing gene expression (for in vivo or in vitro diagnosis), and to identify mutations. Transgenic animals that overexpress (I) are models for human metabolic diseases.

Dwg.0/1

L19 ANSWER 2 OF 22 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998010207 EMBASE

TITLE: The 19th annual meeting of the European Lipoprotein Club.

AUTHOR: Stalenhoef A.F.H.; Aalto-Setala K.; Armstrong V.W.; Benlian P.; Dieplinger H.; Humphries S.; Steinmetz A.

CORPORATE SOURCE: Dr. A.F.H. Stalenhoef, Department of Medicine, Div. of General Internal Med. 541, University Hospital

Nijmegen, PO Box 9101, 6500 HB Nijmegen, Netherlands.
A.Stalenhoef@aig.azn.nl
SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology, (1997) 17/11 (2316-2325).
ISSN: 1079-5642 CODEN: ATVBFA
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
028 Urology and Nephrology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English

L19 ANSWER 3 OF 22 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94133919 EMBASE
DOCUMENT NUMBER: 1994133919
TITLE: A polyol dilution method for mass production of liposomes.
AUTHOR: Kikuchi H.; Yamauchi H.; Hirota S.
CORPORATE SOURCE: Developmental Research Laboratories, Daiichi Pharmaceutical Co., Ltd., 16-13, Kita-Kasai 1-chome,Edogawa-ku, Tokyo 134, Japan
SOURCE: Journal of Liposome Research, (1994) 4/1 (71-91).
ISSN: 0898-2104 CODEN: JLREE7
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We developed a polyol dilution method for the mass production of liposomes. This method consists of the mixing of membrane components (and lipophilic drugs) with a water-soluble, non-volatile organic solvent (glycerin, propylene glycol, etc.), followed by the dispersal of the mixture in an aqueous medium. The polyols which can be used in this method are physiologically acceptable even when the final preparation is administered intravenously into the human body. Liposomes prepared by this polyol dilution method (PD-liposomes) were characterized in comparison with the traditional liposomes known as Bangham's liposomes. Incorporation of cholesterol and charged lipids was confirmed by gel filtration chromatography, differential scanning calorimetry and zeta potential measurements. Homogeneous size distribution of PD-liposomes could be obtained by an extrusion technique. The encapsulation efficiency of

**sodium salicylate** and dextran T-40 as water-soluble model drugs was 4-18%, while a higher encapsulation efficiency could be achieved if the concentrated dextran aqueous solution was previously added to the lipids-polyol mixture and kneaded. This method was applied for the preparation of nascent HDL and liposomal doxorubicin. The polyol dilution method is considered a convenient and valuable technique for the mass production of liposomes.

L19 ANSWER 4 OF 22 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1984:20725 BIOSIS
DOCUMENT NUMBER: BR26:20725
TITLE: CHANGES IN PLASMA PROTEIN BINDING OF DRUGS AFTER BLOOD COLLECTION FROM PREGNANT WOMEN.
AUTHOR(S): CHOU R C; WIEGAND U W; LELE A S; LEVY G
CORPORATE SOURCE: DEP. PHARM., STATE UNIV. N.Y. BUFFALO, AMHERST, N.Y. 14260.
SOURCE: J. Pharm. Sci., (1983) 72 (6), 716-718.
CODEN: JPMSAE. ISSN: 0022-3549.
FILE SEGMENT: BR; OLD
LANGUAGE: English

L19 ANSWER 5 OF 22 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 80002431 EMBASE
DOCUMENT NUMBER: 1980002431
TITLE: Applications and limitations of measurement of 15-keto-13,14-dihydro prostaglandin E2 in human blood by radioimmunoassay.
AUTHOR: Metz S.A.; Rice M.G.; Robertson R.P.
CORPORATE SOURCE: Div. Clin. Pharmacol., VA Med. Cent., Seattle, Wash. 98108, United States
SOURCE: Prostaglandins, (1979) 17/6 (839-861).
CODEN: PRGLBA
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
023 Nuclear Medicine
LANGUAGE: English
AB It has been anticipated that the inherent limitations of radioimmunoassays for prostaglandin E (PGE) would be obviated by assays for its major circulating metabolite, 15-keto, 13,14-dihydro PGE2 (KH2-PGE2) which has a longer half-life in blood. We examined the effects of PGE2 infusion and alterations in **lipolysis** in vivo, and of clotting, prolonged storage and hemolysis in vitro, on KH2-PGE2 immunoreactivity in unextracted human plasma and serum samples. Indeed KH2-PGE2 levels rose several hundred fold during infusions of PGE2 at doses which cause little or no increment in

peripheral PGE levels. During stimulation of **lipolysis** by infusions of epinephrine, apparent KH2-PGE2 levels rose fivefold. However, the dilution curve of plasma obtained during stimulation of **lipolysis** was not parallel to the standard curve; furthermore, apparent KH2-PGE2 levels were correlated strongly with fatty acid (FFA) levels, suggesting that FFA's crossreacted in the RIA weakly but significantly due to their very high molar concentration in blood. Clotting and prolonged storage of samples, but not hemolysis, also caused marked apparent increments in KH2-PGE2 levels. Competition curves using dilutions of such samples were again not parallel to the standard curves in plasma or buffer, but resembled dilution curves of samples containing high levels of FFA. These results suggest that handling of human blood samples for KH2-PGE2 measurement must be carefully standardized to avoid significant artifacts which presumably are due in part to fatty acids released from triglyceride stores in vivo or from disrupted membrane phospholipids in vitro. Unextracted plasma appears to be unsatisfactory for use in this RIA.

L19 ANSWER 6 OF 22 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 80123855 MEDLINE
DOCUMENT NUMBER: 80123855 PubMed ID: 531484
TITLE: Effect of myocardial ischaemia and antilipolytic agents on **lipolysis** and fatty acid metabolism in the in situ dog heart.
AUTHOR: Vik-Mo H; Riemersma R A; Mjos O D; Oliver M F
SOURCE: SCANDINAVIAN JOURNAL OF CLINICAL AND LABORATORY INVESTIGATION, (1979 Oct) 39 (6) 559-68.
Journal code: UCP; 0404375. ISSN: 0036-5513.
PUB. COUNTRY: Norway
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198004
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19980206
Entered Medline: 19800423

AB Myocardial metabolism was studied in open-chest dogs before and during induction of myocardial ischaemia by coronary artery occlusion. Blood was sampled from a local coronary vein draining ischaemic tissue and from coronary sinus draining predominantly nonischaemic tissue. In the basal state, induction of myocardial ischaemia stimulated myocardial **lipolysis** as shown by release of glycerol from the ischaemic zone. During isoprenaline infusion, free fatty acids (FFA) extraction across the ischaemic myocardium was substantially increased, but no glycerol release occurred. Pretreatment with nicotinic acid or **sodium salicylate** markedly depressed FFA extraction across

ischaemic myocardium, both during basal and isoprenaline stimulated **lipolysis** and nicotinic acid most likely inhibited **lipolysis** in the ischaemic zone. Thus, reduced severity of acute ischaemic injury by antilipolytic treatment might be due to a combination of inhibited myocardial **lipolysis** and reduced FFA extraction.

L19 ANSWER 7 OF 22 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 80113653 EMBASE
DOCUMENT NUMBER: 1980113653
TITLE: Effect of myocardial ischaemia and antilipolytic agents on **lipolysis** and fatty acid metabolism in the in situ dog heart.
AUTHOR: Vik-Mo H.; Riemersma R.A.; Mjos O.D.; Oliver M.F.
CORPORATE SOURCE: Inst. Med. Biol., Univ. Tromso, Norway
SOURCE: European Journal of Clinical Investigation, (1979) 9/2 II (225).
CODEN: EJCIB8
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English

L19 ANSWER 8 OF 22 MEDLINE
ACCESSION NUMBER: 78204021 MEDLINE
DOCUMENT NUMBER: 78204021 PubMed ID: 663543
TITLE: Mechanisms for inhibition of free fatty acid mobilization by nicotinic acid and **sodium salicylate** in canine subcutaneous adipose tissue in situ.
AUTHOR: Vik-Mo H; Mjos O D
SOURCE: SCANDINAVIAN JOURNAL OF CLINICAL AND LABORATORY INVESTIGATION, (1978 May) 38 (3) 209-16.
Journal code: UCP; 0404375. ISSN: 0036-5513.
PUB. COUNTRY: Norway
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197808
ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19780814
AB Mechanisms for reduced free fatty acids (FFA) mobilization effected by nicotinic acid (NA) and **sodium salicylate** (SS) were studied in canine adipose tissue in situ. Both drugs inhibited adipose tissue **lipolysis** as evidenced by reduced release of glycerol. In addition, although the total amount of FFA re-esterified was not significantly changed, the amount of FFA

re-esterified relative to the amount of FFA liberated intracellularly was significantly increased by both drugs. These effects were most pronounced during isoprenaline-stimulated **lipolysis**. Thus NA and SS reduced mobilization of FFA from canine adipose tissue through a combined effect on re-esterification and **lipolysis**.

L19 ANSWER 9 OF 22 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 78359643 EMBASE
DOCUMENT NUMBER: 1978359643
TITLE: Mechanisms for inhibition of free fatty acid mobilization by nicotinic acid and **sodium salicylate** in canine subcutaneous adipose tissue in situ.
AUTHOR: Vik Mo H.; Mjos O.D.
CORPORATE SOURCE: Inst. Med. Biol., Physiol. Sect., Univ. Tromso, Norway
SOURCE: Scandinavian Journal of Clinical and Laboratory Investigation, (1978) 38/3 (209-216).
CODEN: SJCLAY
COUNTRY: Norway
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
029 Clinical Biochemistry
LANGUAGE: English
AB Mechanisms for reduced free fatty acid (FFA) mobilization effected by nicotinic acid (NA) and **sodium salicylate** (SS) were studied in canine adipose tissue in situ. Both drugs inhibited adipose tissue **lipolysis** as evidenced by reduced release of glycerol. In addition, although the total amount of FFA re-esterified was not significantly changed, the amount of FFA re-esterified relative to the amount of FFA liberated intracellularly was significantly increased by both drugs. These effects were most pronounced during isoprenaline-stimulated **lipolysis**. Thus NA and SS reduced mobilization of FFA from canine adipose tissue through a combined effect on re-esterification and **lipolysis**.

L19 ANSWER 10 OF 22 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 78231809 MEDLINE
DOCUMENT NUMBER: 78231809 PubMed ID: 676763
TITLE: Effects of **sodium salicylate** on plasma insulin concentration and fatty acid turnover in dogs.
AUTHOR: Vik-Mo H; Hove K; Mjos O D
SOURCE: ACTA PHYSIOLOGICA SCANDINAVICA, (1978 Jun) 103 (2) 113-9.

Journal code: 1U4; 0370362. ISSN: 0001-6772.
PUB. COUNTRY: Sweden
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197809
ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19780925

AB The effects of intravenous **sodium salicylate** administration on plasma concentrations of insulin, free fatty acids (FFA) and glucose were studied in intact, anaesthetized dogs both during basal and isoprenaline stimulated **lipolysis**. In both situations **sodium salicylate** reduced the plasma concentrations of insulin. The reduction was associated with decreased plasma FFA concentrations and FFA turnover rate, while plasma glucose concentrations remained unaltered. The reduced plasma insulin concentrations effected by **sodium salicylate** is most likely secondary to the concomitant fall in plasma FFA concentrations due to inhibition of FFA mobilization from adipose tissue.

L19 ANSWER 11 OF 22 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 77150686 EMBASE
DOCUMENT NUMBER: 1977150686
TITLE: [Caffeine stimulated **lipolysis** and pathological pregnancy].
STELLENWERT DER COFFEINSTIMULIERTEN **LIPOLYSE** IM RAHMEN DER PATHOLOGISCHEN SCHWANGERSCHAFT.
AUTHOR: Riemer W.D.; Prott V.; Franke G.
CORPORATE SOURCE: Frauenklin., Ber. Med., Ernst Moritz Arndt Univ., Greifswald, Germany
SOURCE: Zentralblatt fur Gynakologie, (1976) 98/18 (1137-1143).
CODEN: ZEGYAX
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
010 Obstetrics and Gynecology
030 Pharmacology
LANGUAGE: German

AB In an acute experiment the effect of caffeine Sodium salicylicum (3 mg/kg body weight) on the parameter of **lipolysis** of free fatty acids (FFA) and free glycerin in early pregnancy is investigated. On the base of literature data the possibility of labour induction due to high blood values of FFA and glycerin is explained and the importance of caffeine stimulated **lipolysis** in pregnancy is discussed. To prevent one possible cause of abortus or miscarriage it is recommended to restrict taking

coffee during pregnancy.

L19 ANSWER 12 OF 22 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 78054534 MEDLINE
DOCUMENT NUMBER: 78054534 PubMed ID: 1031488
TITLE: Myocardial metabolism and performance during **sodium salicylate** infusion in dogs.
AUTHOR: Vik-Mo H; Mjos O D
SOURCE: SCANDINAVIAN JOURNAL OF CLINICAL AND LABORATORY INVESTIGATION, (1976 Dec) 36 (8) 763-9.
Journal code: UCP; 0404375. ISSN: 0036-5513.
PUB. COUNTRY: Norway
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197801
ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19980206
Entered Medline: 19780127

AB The effect of **sodium salicylate** on net myocardial free fatty acid (FFA) uptake, myocardial oxygen consumption (MVO2), and the mechanical activity of the heart was studied in eight intact, anesthetized dogs. **Sodium salicylate** was given intravenously under basal conditions and during isoproterenol-stimulated **lipolysis**. Under basal conditions, **sodium salicylate** significantly reduced arterial FFA concentration, but did not influence net myocardial uptake of FFA, and MVO2 was unchanged. During isoproterenol infusion **sodium salicylate** reduced arterial FFA concentration 28% (P less than 0.01) and significantly reduced net myocardial uptake of FFA from 44.5 +/- 9.0 (mean +/- S.E.M.) to 22.3 +/- 2.1 mumol/min-100g tissue (P less than 0.05) and MVO2 from 20.3 +/- 2.2 to 160 +/- 1.9 ml/min-100g tissue (P less than 0.05). The reduction in MVO2 could not be explained by reduced mechanical activity of the heart. Most probably the mechanism for the reduction in MVO2 effected by **sodium salicylate** during isoproterenol infusion was mediated by reduced myocardial FFA consumption.

L19 ANSWER 13 OF 22 EMBASE 
ACCESSION NUMBER: 78062967 EMBASE
DOCUMENT NUMBER: 1978062967
TITLE: Myocardial metabolism and performance during **sodium salicylate** infusion in dogs.
AUTHOR: Vik Mo H.; Mjos O.D.
CORPORATE SOURCE: Sect. Physiol., Inst. Med. Biol., Univ. Tromso, Norway
SOURCE: Scandinavian Journal of Clinical and Laboratory

Investigation, (1976) 36/8 (763-769).
CODEN: SJCLAY
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
018 Cardiovascular Diseases and Cardiovascular Surgery
019 Rehabilitation and Physical Medicine
030 Pharmacology
LANGUAGE: English

L19 ANSWER 14 OF 22 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 77102325 MEDLINE
DOCUMENT NUMBER: 77102325 PubMed ID: 1012973
TITLE: Studies on antilipolytic activity of antipyretics. Part II. Influence of **sodium salicylate**, aminophenazone, and acetophenidin on **lipolysis** stimulated by noradrenaline and aminophylline in vitro.
AUTHOR: Matuszek M
SOURCE: POLISH JOURNAL OF PHARMACOLOGY AND PHARMACY, (1976) 28 (5) 437-42.
Journal code: PB0; 0366561. ISSN: 0301-0244.
PUB. COUNTRY: Poland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197703
ENTRY DATE: Entered STN: 19900313
Last Updated on STN: 19900313
Entered Medline: 19770321

AB **Lipolysis**, expressed as muEq of FFA released from 1 g of epididymal fat tissue per hour, was stimulated by noradrenaline (NA) and aminophyline. **Sodium salicylate** inhibited the **lipolysis** stimulated by NA, but not by aminophylline. Aminophenazone and acetophenidin inhibited the **lipolysis** stimulated either by NA or by aminophylline. The antipyretics inhibited stimulated **lipolysis** in a non-competitive manner. The results suggest an important role of the action of antipyretics on **lipolysis** in their hypothermizing action.

L19 ANSWER 15 OF 22 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 77102324 MEDLINE
DOCUMENT NUMBER: 77102324 PubMed ID: 796833
TITLE: Studies on antilipolytic activity of antipyretics. Part I. Influence of **sodium salicylate**, acetylsalicylic acid, phenazone, aminophenazone, and acetophenidin on **lipolysis** in fever induced by E. coli

pyrogen.
AUTHOR: Matuszek M
SOURCE: POLISH JOURNAL OF PHARMACOLOGY AND PHARMACY, (1976) 28 (5) 429-35.
Journal code: PB0; 0366561. ISSN: 0301-0244.
PUB. COUNTRY: Poland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197703
ENTRY DATE: Entered STN: 19900313
Last Updated on STN: 19980206
Entered Medline: 19770321

AB The fever induced by E. coli pyrogen (LPS) is accompanied by a rise of FFA and glycerol level. All tested antipyretics inhibited both thermogenesis of **lipolysis** produced by LPS. These results suggest that the antipyretic effect of antipyretic drugs is not confined to their action on heat-dissipating mechanisms, but may also be exerted by a depression of lipid metabolism.

L19 ANSWER 16 OF 22 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1977:27272 BIOSIS
DOCUMENT NUMBER: BR13:27272
TITLE: **LIPOLYSIS** IN THE PIG EFFECTS OF PORCINE PITUITARY PEPTIDES.
AUTHOR(S): HERTELENDY F; TODD H
SOURCE: J. Anim. Sci., (1976) 43 (1), 289.
CODEN: JANSAG. ISSN: 0021-8812.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: Unavailable

L19 ANSWER 17 OF 22 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 77133431 EMBASE
DOCUMENT NUMBER: 1977133431
TITLE: Effects of **sodium salicylate** on myocardial metabolism in intact dogs.
AUTHOR: Vik Mo H.; Mjos O.D.
CORPORATE SOURCE: Inst. Med. Biol., Univ. Tromso, Norway
SOURCE: European Journal of Clinical Investigation, (1976) 6/4 (no.187).
CODEN: EJCIB8
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English

L19 ANSWER 18 OF 22 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 78016302 EMBASE

DOCUMENT NUMBER: 1978016302
TITLE: Combined vessel injury action of adjuvant arthritis and cholesterol feeding. II. The influence of different types of drugs on the new model of experimental atherosclerosis.
AUTHOR: Virag S.; Vertesi C.; Welner I.
CORPORATE SOURCE: Dept. Pharmacol. Toxicol., Chinoin Chem. Pharmaceut. Works, Budapest, Hungary
SOURCE: Therapia Hungarica, (1976) 24/4 (142-144).
CODEN: THHUAF
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
LANGUAGE: English
AB Vascular injury suggestive of atheroslerosis associated with considerable lipid deposition was induced in rats suffering from adjuvant arthritis and receiving cholesterol containing food. The inflammatory reaction and the development of vascular injury associated with lipid deposition were moderated to the expected degree in response to indomethacin and **Na salicylate** administration. Clofibrate prevents the deposition of lipid accompanying inflammatory reaction. This model seems to be suitable for testing vasoprotective agents with different mechanism of action.

L19 ANSWER 19 OF 22 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 6
ACCESSION NUMBER: 1974:132281 BIOSIS
DOCUMENT NUMBER: BA57:31981
TITLE: CHOLERA TOXIN FAT CELL INTERACTION AND THE MECHANISM OF ACTIVATION OF THE **LIPOLYTIC** RESPONSE.
AUTHOR(S): CUATRECASAS P
SOURCE: BIOCHEMISTRY, (1973) 12 (18), 3567-3577.
CODEN: BICHAW. ISSN: 0006-2960.
FILE SEGMENT: BA; OLD
LANGUAGE: Unavailable

L19 ANSWER 20 OF 22 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 73142179 MEDLINE
DOCUMENT NUMBER: 73142179 PubMed ID: 4348116
TITLE: Effects of **sodium salicylate** and acetylsalicylic acid on the **lipolytic** system of fat cells.
AUTHOR: Schonhofer P S; Sohn J; Peters H D; Dinnendahl V
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1973 Mar 1) 22 (5) 629-37.
Journal code: 9Z4; 0101032. ISSN: 0006-2952.
PUB. COUNTRY: United States

Searcher : Shears 308-4994

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197305
ENTRY DATE: Entered STN: 19900310
Last Updated on STN: 19900310
Entered Medline: 19730515

L19 ANSWER 21 OF 22 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1973:6599 BIOSIS
DOCUMENT NUMBER: BR09:6599
TITLE: MECHANISM OF THE ANTI **LIPOLYTIC** ACTION OF SALICYLATES.
AUTHOR(S): SCHOENHOEFER P S; PETERS H-D; DINNENDAHL V; KARZEL K
SOURCE: Naunyn-Schmiedeberg's Arch. Pharmacol., (1972) 274 (SUPPL), R101.
CODEN: NSAPCC. ISSN: 0028-1298.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: Unavailable

L19 ANSWER 22 OF 22 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 69214650 MEDLINE
DOCUMENT NUMBER: 69214650 PubMed ID: 4182513
TITLE: Effect of **sodium salicylate** on induced **lipolysis** in isolated fat cells of the rat.
AUTHOR: Stone D B; Brown J D; Steele A A
SOURCE: METABOLISM: CLINICAL AND EXPERIMENTAL, (1969 Jul) 18 (7) 620-4.
Journal code: MUM; 0375267. ISSN: 0026-0495.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 196908
ENTRY DATE: Entered STN: 19900101
Last Updated on STN: 19980206
Entered Medline: 19690806

FILE 'MEDLINE' ENTERED AT 12:44:42 ON 05 SEP 2001
L20 1154 SEA FILE=MEDLINE ABB=ON PLU=ON "SODIUM SALICYLATE"/CT
L21 3306 SEA FILE=MEDLINE ABB=ON PLU=ON LIPOLYSIS/CT
L22 2596 SEA FILE=MEDLINE ABB=ON PLU=ON "RNA, CATALYTIC"/CT
L23 1 SEA FILE=MEDLINE ABB=ON PLU=ON L21 AND (L20 OR L22)

L21 3306 SEA FILE=MEDLINE ABB=ON PLU=ON LIPOLYSIS/CT

Searcher : Shears 308-4994

L24 10881 SEA FILE=MEDLINE ABB=ON PLU=ON PHOSPHOTRANSFERASES/CT
L25 1 SEA FILE=MEDLINE ABB=ON PLU=ON L21 AND L24

L21 3306 SEA FILE=MEDLINE ABB=ON PLU=ON LIPOLYSIS/CT
L26 4164 SEA FILE=MEDLINE ABB=ON PLU=ON "MITOGEN-ACTIVATED PROTEIN KINASES"/CT
L27 1 SEA FILE=MEDLINE ABB=ON PLU=ON L26 AND L21

L28 [illegible] L25 OR L27

L28 ANSWER 1 OF 3 MEDLINE
AN 2001148424 MEDLINE
TI Distinct long-term regulation of glycerol and non-esterified fatty acid release by insulin and TNF-alpha in 3T3-L1 adipocytes.
AU Rosenstock M; Greenberg A S; Rudich A
SO DIABETOLOGIA, (2001 Jan) 44 (1) 55-62.
Journal code: E93; 0006777. ISSN: 0012-186X.
AB AIMS/HYPOTHESIS: Adipose tissue lipolysis plays a central part in total body fuel metabolism. Our study was to assess the long-term regulation of glycerol and non-esterified fatty acid (NEFA) release by insulin or TNF-alpha. METHODS: Fully differentiated 3T3-L1 adipocytes were exposed for up to 22 h to insulin or TNF-alpha. RESULTS: Long-term insulin treatment resulted in increased basal glycerol release, reaching sixfold at 22 h with 1 nmol/l insulin. Partial inhibition was observed by pharmacologically inhibiting phosphatidylinositol 3-kinase or the mitogen-activated kinase kinase--extracellular signal-regulated kinase cascades. This represented 50-60% of the response induced by 1 nmol/l TNF-alpha and approximately 40 % of the glycerol release maximally stimulated by isoproterenol (1 micromol/l, 30 min). The cellular mechanism seemed to be distinct from that of TNF-alpha: First, glycerol release in response to long-term insulin was progressive with time and did not display a lag-time characteristic of the effect of TNF-alpha. Second, pretreatment and co-treatment of the cells with troglitazone greatly inhibited TNF-alpha-induced glycerol release (128.5 +/- 10.2 to 35.4 +/- 2.1 nmol/mg protein per h) but not the effect of insulin, which was exaggerated. Third, hormone-sensitive lipase protein content was decreased (45 %) by TNF-alpha but not following long-term insulin. Finally, TNF-alpha was associated with NEFA release to the medium, whereas long-term insulin treatment was not. Moreover, glycerol release during isoproterenol-stimulated lipolysis was additive to the effect of long-term insulin, whereas NEFA release was inhibited by nearly 90 %. CONCLUSIONS INTERPRETATION: Contradictory to its short-term inhibitory effect, long-term insulin stimulates glycerol release with concomitant stimulation of NEFA re-esterification.

Searcher : Shears 308-4994

L28 ANSWER 2 OF 3 MEDLINE
AN 88198506 MEDLINE
TI Alterations in insulin receptor autophosphorylation in insulin resistance: correlation with altered sensitivity to glucose transport and antilipolysis to insulin.
AU Takayama S; Kahn C R; Kubo K; Foley J E
SO JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, (1988 May) 66 (5) 992-9.
Journal code: HRB; 0375362. ISSN: 0021-972X.
AB We studied insulin binding, receptor autophosphorylation, and insulin action in isolated adipocytes from 23 Pima Indians with varying degrees of obesity over a range of glucose tolerance. [125I]Insulin binding varied widely and did not correlate with fasting plasma immunoreactive insulin levels or insulin sensitivity, as assessed by the ED50 values of insulin stimulation of glucose transport or insulin inhibition of lipolysis in isolated abdominal wall adipocytes obtained by biopsy from the patients. In contrast there was a significant correlation between loss of stimulation of autophosphorylation in solubilized receptors and loss of insulin sensitivity for both stimulation of glucose transport ($r = -0.59$; $P < 0.005$) and inhibition of lipolysis ($r = -0.54$; $P < 0.01$). There was also a significant inverse correlation between insulin's ability to stimulate receptor autophosphorylation and in vivo insulin resistance, as assessed by fasting plasma insulin levels ($r = -0.46$; $P < 0.05$). These data indicate a significant correlation between changes in sensitivity of glucose transport and antilipolysis to insulin and receptor kinase activity in those patients and suggest that defective coupling of insulin binding to insulin action at the level of phosphorylation of the insulin receptor may cause the insulin resistance in this group of patients.

L28 ANSWER 3 OF 3 MEDLINE
AN 80123855 MEDLINE
TI Effect of myocardial ischaemia and antilipolytic agents on lipolysis and fatty acid metabolism in the in situ dog heart.
AU Vik-Mo H; Riemersma R A; Mjos O D; Oliver M F
SO SCANDINAVIAN JOURNAL OF CLINICAL AND LABORATORY INVESTIGATION, (1979 Oct) 39 (6) 559-68.
Journal code: UCP; 0404375. ISSN: 0036-5513.
AB Myocardial metabolism was studied in open-chest dogs before and during induction of myocardial ischaemia by coronary artery occlusion. Blood was sampled from a local coronary vein draining ischaemic tissue and from coronary sinus draining predominantly nonischaemic tissue. In the basal state, induction of myocardial ischaemia stimulated myocardial lipolysis as shown by release of glycerol from the ischaemic zone. During isoprenaline infusion, free

fatty acids (FFA) extraction across the ischaemic myocardium was substantially increased, but no glycerol release occurred. Pretreatment with nicotinic acid or sodium salicylate markedly depressed FFA extraction across ischaemic myocardium, both during basal and isoprenaline stimulated lipolysis and nicotinic acid most likely inhibited lipolysis in the ischaemic zone. Thus, reduced severity of acute ischaemic injury by antilipolytic treatment might be due to a combination of inhibited myocardial lipolysis and reduced FFA extraction.

[redacted] CAPLUS ENTERED AT 12:53:10 ON 05 SEP 2001
L29 12 SEA ABB=ON PLU=ON ANTILIPOLY? AND (L14 OR L5 OR L7 OR MAPK OR JNK OR ERK#)
L30 4 SEA ABB=ON PLU=ON L29 NOT (L8 OR L15)

L30 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:383088 CAPLUS
DOCUMENT NUMBER: 129:104500
TITLE: Association of the insulin receptor with phospholipase C-.gamma. (PLC.gamma.) in 3T3-L1 adipocytes suggests a role for PLC.gamma. in metabolic signaling by insulin
AUTHOR(S): Kayali, Ayse G.; Eichhorn, Jens; Haruta, Tetsuro; Morris, Aaron J.; Nelson, James G.; Vollenweider, Peter; Olefsky, Jerrold M.; Webster, Nicholas J. G.
CORPORATE SOURCE: UCSD/Whittier Diabetes Program, University of California San Diego, La Jolla, CA, 92093, USA
SOURCE: J. Biol. Chem. (1998), 273(22), 13808-13818
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phospholipase C-.gamma. (PLC.gamma.) is the isoenzyme of PLC phosphorylated by multiple tyrosine kinases including epidermal growth factor, platelet-derived growth factor, nerve growth factor receptors, and nonreceptor tyrosine kinases. In this paper, the authors present evidence for the assocn. of the insulin receptor (IR) with PLC.gamma.. Pptn. of the IR with glutathione S-transferase fusion proteins derived from PLC.gamma. and coimmunopptn. of the IR and PLC.gamma. were obsd. in 3T3-L1 adipocytes. To det. the functional significance of the interaction of PLC.gamma. and the IR, the authors used a specific inhibitor of PLC, U73122, or microinjection of SH2 domain glutathione S-transferase fusion proteins derived from PLC.gamma. to block insulin-stimulated GLUT4 translocation. The authors demonstrate inhibition of 2-deoxyglucose uptake in isolated primary rat

adipocytes and 3T3-L1 adipocytes pretreated with U73122. **Antilipolytic** effect of insulin in 3T3-L1 adipocytes is unaffected by U73122. U73122 selectively inhibits **mitogen -activated** protein **kinase**, leaving the Akt and p70 S6 kinase pathways unperturbed. The authors conclude that PLC.gamma. is an active participant in metabolic and perhaps mitogenic signaling by the insulin receptor in 3T3-L1 adipocytes.

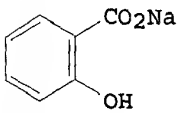
L30 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:11620 CAPLUS
DOCUMENT NUMBER: 128:123964
TITLE: Insulin-induced phosphorylation and activation of phosphodiesterase 3B in rat adipocytes: possible role for protein **kinase** B but not **mitogen-activated** protein **kinase** or p70 S6 **kinase**
AUTHOR(S): Wijkander, Jonny; Landstrom, Tova Rahn; Manganiello, Vincent; Belfrage, Per; Degerman, Eva
CORPORATE SOURCE: Section Mol. Signalling, Lund Univ., Swed.
SOURCE: Endocrinology (1998), 139(1), 219-227
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Insulin stimulation of adipocytes results in serine phosphorylation/activation of phosphodiesterase 3B (PDE 3B) and activation of a kinase that phosphorylates PDE 3B in vitro, key events in the **antilipolytic** action of this hormone. We have investigated the role for p70 S6 **kinase**, **mitogen-activated** protein **kinases** (MAP **kinases**), and protein kinase B (PKB) in the insulin signaling pathway leading to phosphorylation/activation of PDE 3B in adipocytes. Insulin stimulation of adipocytes resulted in increased activity of p70 S6 kinase, which was completely blocked by pretreatment with rapamycin. However, rapamycin had no effect on the insulin-induced phosphorylation/activation of PDE 3B or the activation of the kinase that phosphorylates PDE 3B. Stimulation of adipocytes with insulin or phorbol myristate acetate induced activation of MAP kinases. Pretreatment of adipocytes with the MAP kinase kinase inhibitor PD 98059 was without effect on the insulin-induced activation of PDE 3B. Furthermore, phorbol myristate acetate stimulation did not result in phosphorylation/activation of PDE 3B or activation of the kinase that phosphorylates PDE 3B. Using Mono Q and Superdex chromatog., the kinase that phosphorylates PDE 3B was found to co-elute with PKB, but not with p70 S6 kinase or MAP kinases. Furthermore, both

PKB and the kinase that phosphorylates PDE 3B were found to translocate to membranes in response to peroxovanadate stimulation of adipocytes in a wortmannin-sensitive way. Whereas these results suggest that p70 S6 kinase and MAP kinases are not involved in the insulin-induced phosphorylation/activation of PDE 3B in rat adipocytes, they are consistent with PKB being the kinase that phosphorylates PDE 3B.

IT **142243-02-5**, **Mitogen-activated** protein **kinase 142805-58-1**, MAP kinase kinase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(insulin-induced phosphorylation and activation of phosphodiesterase 3B in rat adipocytes and role for protein **kinase** B but not **mitogen-activated** protein **kinase** or p70 S6 **kinase** therein)

L30 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1980:597643 CAPLUS
DOCUMENT NUMBER: 93:197643
TITLE: The effect of **sodium salicylate** and epinephrine on the release of lactate dehydrogenase from isolated rat heart
AUTHOR(S): Tutterova, M.; Mosinger, B.; Vavrinkova, H.
CORPORATE SOURCE: Cardiovasc. Res. Cent., Inst. Clin. Exp. Med., Prague, 14622, Czech.
SOURCE: Acta Biol. Med. Ger. (1980), 39(4), 433-43
CODEN: ABMGAJ; ISSN: 0001-5318
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



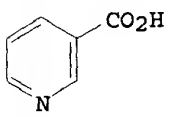
I

AB **Na salicylate** (I) [**54-21-7**] reduced the release of lactate dehydrogenase [9001-60-9] from isolated rat heart and the effect was assocd. with elevated triglyceride levels and a redn. of the heart rate. Lactate [50-21-5] prodn. increased and was accompanied by an increased uptake of glucose [50-99-7] from the medium and increased coronary flow. In the presence of L-adrenaline-HCl (II) [55-31-2] and I only the total no. of heart beats was reduced. Acetylsalicylate [50-78-2] could not mimick the

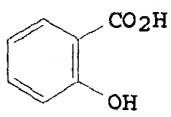
effects of I. Apparently, the effect of I on the heart is due to its **antilipolytic** and neg. chronotropic effects.

IT **54-21-7**
RL: BIOL (Biological study)
(lactate dehydrogenase release from heart by, epinephrine in relation to)

L30 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1979:66599 CAPLUS
DOCUMENT NUMBER: 90:66599
TITLE: Distribution of coronary blood flow during acute coronary occlusion in dogs. Effect of nicotinic acid and **sodium salicylate**
AUTHOR(S): Vik-Mo, Harald
CORPORATE SOURCE: Inst. Med. Biol., Univ. Tromsoe, Tromsoe, Norway
SOURCE: Scand. J. Clin. Lab. Invest. (1977), 37(8), 697-703
CODEN: SJCLAY; ISSN: 0036-5513
DOCUMENT TYPE: Journal
LANGUAGE: English
GI




I




II

AB The effects of the **antilipolytic** agents nicotinic acid (I) and **Na salicylate** (Na II) on the distribution of coronary blood flow during acute myocardial ischemia were studied in open chest dogs. Fifteen min following exptl. coronary artery occlusion, blood flow in the ischemic myocardium was on av. 28% of the flow in the non-ischemic myocardium. The redn. in blood flow in the ischemic myocardium was more pronounced in the endocardial than in epicardial halves of the myocardium. No change in blood flow was obsd. after administration of I or II in either the ischemic or nonischemic part of the myocardium. Both drugs reduced the extent of myocardial ischemic injury as shown by reduced epicardial ST-segment elevations. Arterial concns. of fatty acids were lowered by I or II, whereas the mech. activity of the heart remained unchanged. Thus, the redn. of acute myocardial ischemic injury effected by I or II is not due to changes in myocardial blood flow, but more likely to lower myocardial O demand related to reduced

fatty acid utilization.

IT **54-21-7**
RL: BIOL (Biological study)
(heart circulation response to, in heart ischemia)

[redacted]LINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, [redacted]US, JAPIO' ENTERED AT 12:55:02 ON 05 SEP 2001)

L31 27 S L29

[redacted] 10 S L31 NOT (L9 OR L18)

[redacted] REMOVED)

L33 ANSWER 1 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
ACCESSION NUMBER: 1998:317403 BIOSIS
DOCUMENT NUMBER: PREV199800317403
TITLE: Association of the insulin receptor with phospholipase C-gamma (PLCgamma) in 3T3-L1 adipocytes suggests a role for PLCgamma in metabolic signaling in insulin.
AUTHOR(S): Kayali, Ayse G.; Eichhorn, Jens; Haruta, Tetsuro; Morris, Aaron J.; Nelson, James G.; Vollenweider, Peter; Olefsky, Jerrold M.; Websters, Nicholas J. G. (1)
CORPORATE SOURCE: (1) Dep. Med., Univ. Calif., San Diego, 9500 Gilman Dr., La Jolla, CA 92093-0673 USA
SOURCE: Journal of Biological Chemistry, (May 29, 1998) Vol. 273, No. 22, pp. 13808-13818.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Phospholipase C-gamma (PLCgamma) is the isozyme of PLC phosphorylated by multiple tyrosine kinases including epidermal growth factor, platelet-derived growth factor, nerve growth factor receptors, and nonreceptor tyrosine kinases. In this paper, we present evidence for the association of the insulin receptor (IR) with PLCgamma. Precipitation of the IR with glutathione S-transferase fusion proteins derived from PLCgamma and coimmunoprecipitation of the IR and PLCgamma were observed in 3T3-L1 adipocytes. To determine the functional significance of the interaction of PLCgamma and the IR, we used a specific inhibitor of PLC, U73122, or microinjection of SH2 domain glutathione S-transferase fusion proteins derived from PLCgamma to block insulin-stimulated GLUT4 translocation. We demonstrate inhibition of 2-deoxyglucose uptake in isolated primary rat adipocytes and 3T3-L1 adipocytes pretreated with U73122. **Antilipolytic** effect of insulin in 3T3-L1 adipocytes is unaffected by U73122. U73122 selectively inhibits **mitogen-activated** protein **kinase**, leaving the Akt and p70 S6 kinase pathways unperturbed. We conclude that PLCgamma is an active participant in

metabolic and perhaps mitogenic signaling by the insulin receptor in 3T3-L1 adipocytes.

L33 ANSWER 2 OF 6 MEDLINE
ACCESSION NUMBER: 1998081771 MEDLINE
DOCUMENT NUMBER: 98081771 PubMed ID: 9421418
TITLE: Insulin-induced phosphorylation and activation of phosphodiesterase 3B in rat adipocytes: possible role for protein **kinase** B but not **mitogen-activated** protein **kinase** or p70 S6 **kinase**.
AUTHOR: Wijkander J; Landstrom T R; Manganiello V; Belfrage P; Degerman E
CORPORATE SOURCE: Department of Cell and Molecular Biology, Lund University, Sweden.
SOURCE: ENDOCRINOLOGY, (1998 Jan) 139 (1) 219-27.
Journal code: EGZ; 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 19990129
Entered Medline: 19980115

AB Insulin stimulation of adipocytes results in serine phosphorylation/activation of phosphodiesterase 3B (PDE 3B) and activation of a kinase that phosphorylates PDE 3B in vitro, key events in the **antilipolytic** action of this hormone. We have investigated the role for p70 S6 **kinase**, **mitogen-activated** protein **kinases** (MAP **kinases**), and protein kinase B (PKB) in the insulin signaling pathway leading to phosphorylation/activation of PDE 3B in adipocytes. Insulin stimulation of adipocytes resulted in increased activity of p70 S6 kinase, which was completely blocked by pretreatment with rapamycin. However, rapamycin had no effect on the insulin-induced phosphorylation/activation of PDE 3B or the activation of the kinase that phosphorylates PDE 3B. Stimulation of adipocytes with insulin or phorbol myristate acetate induced activation of MAP kinases. Pretreatment of adipocytes with the MAP kinase kinase inhibitor PD 98059 was without effect on the insulin-induced activation of PDE 3B. Furthermore, phorbol myristate acetate stimulation did not result in phosphorylation/activation of PDE 3B or activation of the kinase that phosphorylates PDE 3B. Using Mono Q and Superdex chromatography, the kinase that phosphorylates PDE 3B was found to co-elute with PKB, but not with p70 S6 kinase or MAP kinases. Furthermore, both PKB and the kinase that phosphorylates PDE 3B were found to translocate to membranes in

response to peroxovanadate stimulation of adipocytes in a wortmannin-sensitive way. Whereas these results suggest that p70 S6 kinase and MAP kinases are not involved in the insulin-induced phosphorylation/activation of PDE 3B in rat adipocytes, they are consistent with PKB being the kinase that phosphorylates PDE 3B.

L33 ANSWER 3 OF 6 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 87065657 EMBASE
DOCUMENT NUMBER: 1987065657
TITLE: [Pharmacological prevention of sudden cardiac death due to acute myocardial infarction].
LES POSSIBILITIES PHARMACOLOGIQUES DE PREVENTION DES ACCIDENTS CONSECUTIFS A UN INFARCTUS DU MYOCARDE.
AUTHOR: Szekeres L.
CORPORATE SOURCE: Institut de Pharmacologie de l'Universite Medicale de Szeged, 6701 Szeged, Hungary
SOURCE: Journal de Pharmacologie, (1986) 17/SUPPL. 2 (65-81).
CODEN: JNPHAG
COUNTRY: France
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: French
SUMMARY LANGUAGE: English
AB Sudden cardiac death (SCD) due to acute myocardial infarction (AMI) is mostly the result of ventricular fibrillation (VP) which is an electrical accident appearing on the basis of electrical instability of the myocardium. In addition to the chronic electrical instability predisposing to ventricular arrhythmias the trigger effect of a precipitating factor also seems necessary which may disrupt the normal sequence of cardiac contractions. In view of this hypothesis the following strategy of therapeutic interventions aimed at preventing SCD from AMI seems to be logical: 1) Prophylactic measures to prevent pathological processes underlying chronic electrical instability of the heart, i.e. elimination to identified risk factors of ischemic heart disease. 2) Protection from SCD due to AMI. Sudden cardiac death due to acute myocardial infarction is not inevitable; its immediate cause, ventricular fibrillation, is reversible and can be prevented.

L33 ANSWER 4 OF 6 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 87028775 EMBASE
DOCUMENT NUMBER: 1987028775
TITLE: Theoretical basis of **antilipolytic** and phospholipase inhibitory therapy in acute myocardial ischaemia.

AUTHOR: Fazekas T.; Papp G.; Szekeres L.
CORPORATE SOURCE: Institute of Pharmacology, University Medical School, Szeged, Hungary
SOURCE: Therapia Hungarica, (1986) 34/1 (6-16).
CODEN: THHUAF
COUNTRY: Hungary
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: German

L33 ANSWER 5 OF 6 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 81081905 MEDLINE
DOCUMENT NUMBER: 81081905 PubMed ID: 7445893
TITLE: The effect of **sodium salicylate** and epinephrine on the release of lactate dehydrogenase from isolated rat heart.
AUTHOR: Tutterova M; Mosinger B; Vavrinkova H
SOURCE: ACTA BIOLOGICA ET MEDICA GERMANICA, (1980) 39 (4) 433-43.
Journal code: 0E6; 0370276. ISSN: 0001-5318.
PUB. COUNTRY: GERMANY, EAST: German Democratic Republic
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198102
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19810224

AB The isolated perfused rat heart was used to study the effect of therapeutic concentrations of **sodium salicylate** and acetylsalicylate with respect to their potential cardioprotective property described in some clinical studies and experiments in vivo. Salicylates were added to the perfusion medium (Krebs-Henseleit buffer plus 5.5 mM glucose) in final concentrations ranging from 0.1 to 3.2 mM. In lower concentrations **sodium salicylate** reduced release of lactate dehydrogenase from the heart associated with delayed cleavage of endogenous triglycerides and a reduction of heart rate. A significant increase in lactate production, undoubtedly an expression of the uncoupling effect of **sodium salicylate** noted at 1.6 mM or higher concentration was accompanied by an increased uptake of glucose from the medium and increased coronary flow. In the presence of epinephrine (5.5 microM) **sodium salicylate** (0.1 and 0.5 mM) reduced only the total number of heart beats. Equimolar doses of acetylsalicylic acid failed to mimick salicylate effects. The results suggest that potentially cardioprotective effects of salicylate followed in these experiments by myocardial membrane

leakage may be in part explained by the direct action of salicylate on the myocardium due to its **antilipolytic** and negative chronotropic effect. We failed to demonstrate this protective effect of salicylate against cardiotoxic doses of exogenous epinephrine.

L33 ANSWER 6 OF 6 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 78096303 MEDLINE
DOCUMENT NUMBER: 78096303 PubMed ID: 601512
TITLE: Distribution of coronary blood flow during acute coronary occlusion in dogs. Effect of nicotinic acid and **sodium salicylate**.
AUTHOR: Vik-Mo H
SOURCE: SCANDINAVIAN JOURNAL OF CLINICAL AND LABORATORY INVESTIGATION, (1977 Dec) 37 (8) 697-703.
Journal code: UCP; 0404375. ISSN: 0036-5513.
PUB. COUNTRY: Norway
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197803
ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19780329

AB The effects of the **antilipolytic** agents nicotinic acid (NA) and **sodium salicylate** (SS) on the distribution of coronary blood flow during acute myocardial ischaemia were studied in open chest dogs. Fifteen min following experimental coronary artery occlusion, blood flow in the ischaemic myocardium was on average 28% of flow in the non-ischaemic myocardium. The reduction in blood flow in the ischaemic mycardium was more pronounced in the endocardial than in epicardial halves of the myocardium. No significant change in blood flow was observed after administration of NA or SS in either the ischemic or nonischemic part of the myocardium. Both drugs reduced the extent of myocardial ischaemic injury as shown by reduced epicardial ST-segment elevations. Arterial concentrations of fatty acids were lowered by NA or SS, whereas the mechanical activity of the heart remained unchanged. It is concluded that the reduction of acute myocardial ischaemic injury effected by NA or SS is not due to changes in myocardial blood flow, but more likely to lower myocardial oxygen demand related to reduced fatty acid utilization.

FILE 'HOME' ENTERED AT 12:57:13 ON 05 SEP 2001

phosphodiesterase kinase in rat adipocytes)

L8 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:584991 CAPLUS
DOCUMENT NUMBER: 127:273050
TITLE: Selective modification of insulin action in adipose tissue by hyperthyroidism
AUTHOR(S): Fryer, L. G. D.; Holness, M. J.; Sugden, M. C.
CORPORATE SOURCE: Department Biochemistry, Basic Medical Sciences,St. Bartholomew's and the Royal London School Medicine and Dentistry, Queen Mary and Westfield College, London, E1 4NS, UK
SOURCE: J. Endocrinol. (1997), 154(3), 513-522
CODEN: JOENAK; ISSN: 0022-0795
PUBLISHER: Journal of Endocrinology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Adipose-tissue **lipolysis** (assessed from glycerol release) and glucose uptake were examd. in parametrial and mesenteric adipocytes prepd. from control or hyperthyroid rats in relation to changs in insulin sensitivity. Basal rates of **lipolysis** did not differ significantly between adipose-tissue depots. **Lipolysis** was maximally stimulated by noradrenaline at 1 .mu.M, half-maximal anti-**lipolytic** effects of insulin were obsd. at approx. 11 .mu.U/mL insulin, and half-maximal stimulation of glucose uptake was obsd. at approx. 16 .mu.U/mL insulin in adipocytes from both depots. Wortmannin caused a dose-dependent inhibition of the anti-**lipolytic** effect of insulin (150 .mu.U/mL) on noradrenaline-stimulated **lipolysis**. Half-maximal effects of wortmannin were obsd. at 20-40 nM. The p70S6K inhibitor rapamycin and the **mitogen activated protein kinase kinase** inhibitor PD098059 had no effects on noradrenaline-stimulated **lipolysis**. Hyperthyroidism increased basal rats of **lipolysis** and the maximal response of **lipolysis** to noradrenaline stimulation (3.1-fold, and 2.1-fold, resp.) in parametrial adipocytes. Hyperthyroidism markedly blunted the sensitivity of noradrenaline-stimulated **lipolysis** to half-maximal suppression by insulin in both parametrial and mesenteric adipocyte depots, and noradrenaline-stimulated **lipolysis** at a maximal insulin concn. remained significantly higher in adipocytes prepd. from hyperthyroid rats compared with controls. Hyperthyroidism had no effect on basal and little effect on insulin-stimulated glucose uptake. Tri-iodothyronine administered at a low dose selectively influenced the anti-**lipolytic** action of insulin in parametrial adipocytes, and led to significantly less marked elevation in plasma non-esterified fatty acid concns. in vivo. The results demonstrate a selective

effect of hyperthyroidism to impair insulin's anti-**lipolytic** action, and are consistent with the operation of different downstream signaling mechanism for the effects of insulin on adipocyte glucose transport and **lipolysis**.

IT **142805-58-1, Mitogen activated** protein **kinase kinase**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(selective modification of insulin action in adipose tissue by hyperthyroidism)

L8 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:436885 CAPLUS
DOCUMENT NUMBER: 127:131393
TITLE: Functional consequences of constitutively active .alpha.2A-adrenergic receptor expression in 3T3F442A preadipocytes and adipocytes
AUTHOR(S): Betuing, Sandrine; Valet, Philippe; Lapalu, Sophie; Peyroulan, Delphine; Hickson, Gilles; Daviaud, Daniele; Lafontan, Max; Saulnier-Blache, Jean Sebastien
CORPORATE SOURCE: I.N.S.E.R.M U317, Inst. Federatif de Recherches Louis Bugnard, Univ. Paul Sabatier, Toulouse, 31403, Fr.
SOURCE: Biochem. Biophys. Res. Commun. (1997), 235(3), 765-773
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The functional consequences of a constitutively active mutated (CAM) human .alpha.2C10-adrenergic receptor (AR) stably expressed in the 3T3F442A preadipose cell line were analyzed at both preadipocyte and adipocyte stages. At the preadipocyte stage, CAM.alpha.2C10-AR reproduced (in the absence of agonist) and amplified (in the presence of agonist) most of the cellular responses promoted by agonist-stimulated wild type .alpha.2C10-AR (increased preadipocyte proliferation, tyrosyl-phosphorylation of the **Mitogen Activated** Protein **Kinases**, resistance to serum-deprivation-induced cell retraction, inhibition of differentiation). In contrast, at the adipocyte stage, CAM.alpha.2C10-AR expression did not reproduce nor amplify the .alpha.2-adrenergic-dependent antilipolysis, but conversely led to a down-regulation of .alpha.i subunits of the Gi proteins and to an increase in the maximal response to **lipolytic** agents. Our results indicate that long term activation of intracellular signals by CAM-receptors not only lead to the expected cellular responses normally generated by agonist-stimulated wild type receptors, but

can also lead to unexpected responses resulting from long term compensatory adaptations.

L8 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:149657 CAPLUS
DOCUMENT NUMBER: 124:221284
TITLE: .alpha.2A-adrenergic regulation of cyclic AMP accumulation and **lipolysis** in human omental and subcutaneous adipocytes
AUTHOR(S): Vikman, H-L; Savola, J-M; Raasmaja, A; Ohisalo, JJ
CORPORATE SOURCE: Department Medical Chemistry, University Helsinki, Helsinki, Finland
SOURCE: Int. J. Obes. (1996), 20(2), 185-9
CODEN: IJOBDP; ISSN: 0307-0565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Mitogen-activated** protein **kinase**, and a rapid increase in intracellular Ca2+ coupled with reversible cell differences were examd. in .alpha.2-adrenergic regulation between s.c. and omental adipocytes which could offer a possibility of pharmacol. intervention in the metabolic syndrome. Both s.c. and omental adipocytes were isolated from 32 patients. Adipocytes were incubated in the presence of adrenoceptor agonists, and cAMP and glycerol levels were measured. .alpha.2-Adrenoceptors of isolated plasma membranes were characterized. Adrenaline increased cAMP levels about two-fold in omental adipocytes but had almost no effect in s.c. fat cells. The inhibition of cAMP accumulation and glycerol release by UK-14304 and dexmedetomidine was less pronounced in omental adipocytes. The maximal effect of isoprenaline on cAMP levels and glycerol release was similar at the two sites. The s.c. and omental .alpha.-adrenoceptors had similar affinities to 3H-RX821002 and showed characteristics of the .alpha.2A subtype. The receptor densities were 220 and 460 fmol/mg of protein in omental and s.c. membranes, resp. Inhibition of cAMP accumulation and **lipolysis** by .alpha.2A-adrenoceptors is less pronounced in omental than s.c. adipocytes which could be due to differences in receptor no. These differences in .alpha.2A-adrenergic regulation could be of value in the treatment of the metabolic syndrome.

[redacted]LINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, [redacted], JAPIO' ENTERED AT 12:37:24 ON 05 SEP 2001)
57 S L8
L10 [redacted] (33 DUPLICATES REMOVED)

L10 ANSWER 1 OF 24 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001278587 EMBASE

Searcher : Shears 308-4994

TITLE: The biogenesis and functions of lipid bodies in animals, plants and microorganisms.
AUTHOR: Murphy D.J.
CORPORATE SOURCE: D.J. Murphy, Lipoprotein Research Centre, 81 Christchurch Road, Norwich NR2 3NG, United Kingdom. murphy.denis@btinternet.com
SOURCE: Progress in Lipid Research, (2001) 40/5 (325-438). Refs: 767
ISSN: 0163-7827 CODEN: PLIRDW
PUBLISHER IDENT.: S 0163-7827(01)00013-3
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English

L10 ANSWER 2 OF 24 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001148424 MEDLINE
DOCUMENT NUMBER: 21076094 PubMed ID: 11206412
TITLE: Distinct long-term regulation of glycerol and non-esterified fatty acid release by insulin and TNF-alpha in 3T3-L1 adipocytes.
AUTHOR: Rosenstock M; Greenberg A S; Rudich A
CORPORATE SOURCE: The S. Daniel Abraham Center for Health and Nutrition, Department of Clinical Biochemistry, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.
CONTRACT NUMBER: DK50647 (NIDDK)
P30 DK34928 (NIDDK)
SOURCE: DIABETOLOGIA, (2001 Jan) 44 (1) 55-62.
Journal code: E93; 0006777. ISSN: 0012-186X.
PUB. COUNTRY: Germany: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315

AB AIMS/HYPOTHESIS: Adipose tissue **lipolysis** plays a central part in total body fuel metabolism. Our study was to assess the long-term regulation of glycerol and non-esterified fatty acid (NEFA) release by insulin or TNF-alpha. METHODS: Fully differentiated 3T3-L1 adipocytes were exposed for up to 22 h to insulin or TNF-alpha. RESULTS: Long-term insulin treatment resulted in increased basal glycerol release, reaching sixfold at 22 h with 1 nmol/l insulin. Partial inhibition was observed by pharmacologically inhibiting phosphatidylinositol 3-**kinase** or the **mitogen-activated kinase kinase**

--extracellular **signal-regulated kinase** cascades. This represented 50-60% of the response induced by 1 nmol/l TNF-alpha and approximately 40 % of the glycerol release maximally stimulated by isoproterenol (1 micromol/l, 30 min). The cellular mechanism seemed to be distinct from that of TNF-alpha: First, glycerol release in response to long-term insulin was progressive with time and did not display a lag-time characteristic of the effect of TNF-alpha. Second, pretreatment and co-treatment of the cells with troglitazone greatly inhibited TNF-alpha-induced glycerol release (128.5 +/- 10.2 to 35.4 +/- 2.1 nmol/mg protein per h) but not the effect of insulin, which was exaggerated. Third, hormone-sensitive lipase protein content was decreased (45 %) by TNF-alpha but not following long-term insulin. Finally, TNF-alpha was associated with NEFA release to the medium, whereas long-term insulin treatment was not. Moreover, glycerol release during isoproterenol-stimulated **lipolysis** was additive to the effect of long-term insulin, whereas NEFA release was inhibited by nearly 90 %. CONCLUSIONS INTERPRETATION: Contradictory to its short-term inhibitory effect, long-term insulin stimulates glycerol release with concomitant stimulation of NEFA re-esterification.

L10 ANSWER 3 OF 24 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000041655 EMBASE
TITLE: Pasteurella multocida toxin stimulates **mitogen-activated** protein **kinase** via G(q/11)-dependent transactivation of the epidermal growth factor receptor.
AUTHOR: Seo B.; Choy E.W.; Maudsley S.; Miller W.E.; Wilson B.A.; Luttrell L.M.
CORPORATE SOURCE: L.M. Luttrell, Dept. of Medicine, Box 3821, Duke University Medical Center, Durham, NC 27710, United States. luttrell@receptor-biol.duke.edu
SOURCE: Journal of Biological Chemistry, (21 Jan 2000) 275/3 (2239-2245).
Refs: 43
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The dermatonecrotic toxin produced by Pasteurella multocida is one of the most potent mitogenic substances known for fibroblasts in vitro. Exposure to recombinant P. multocida toxin (rPMT) causes phospholipase C-mediated hydrolysis of inositol phospholipids, calcium mobilization, and activation of protein kinase C via a poorly characterized mechanism involving G(q/11) family

heterotrimeric G proteins. To determine whether the regulation of G protein pathways contributes to the mitogenic effects of rPMT, we have examined the mechanism whereby rPMT stimulates the **Erk** **mitogen-activated** protein **kinase** cascade in cultured HEK-293 cells. Treatment with rPMT resulted in a dose and time-dependent increase in **Erk** 1/2 phosphorylation that paralleled its stimulation of inositol phospholipid hydrolysis. Both rPMT- and .alpha.-thrombin receptor- stimulated **Erk** phosphorylation were selectively blocked by cellular expression of two peptide inhibitors of G(q/11) signaling, the dominant negative mutant G protein-coupled receptor kinase, GRK2(K220R), and the G(.alpha.q) carboxyl-terminal peptide, G.alpha.(q)-(305- 359). Like .alpha.-thrombin receptor-mediated **Erk** activation, the effect of rPMT was insensitive to the protein kinase C inhibitor GF109203X, but was blocked by the epidermal growth factor receptor-specific tyrphostin, AG1478 and by dominant negative mutants of mSos1 and Ha-Ras. These data indicate that rPMT employs G(q/11) family heterotrimeric G proteins to induce Ras-dependent **Erk** activation via protein kinase C-independent 'transactivation' of the epidermal growth factor receptor.

L10 ANSWER 4 OF 24 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000395645 MEDLINE
DOCUMENT NUMBER: 20378130 PubMed ID: 10923627
TITLE: Pancreastatin modulates insulin signaling in rat adipocytes: mechanisms of cross-talk.
AUTHOR: Gonzalez-Yanes C; Sanchez-Margalet V
CORPORATE SOURCE: Department of Medical Biochemistry and Molecular Biology, School of Medicine, Virgen Macarena University Hospital, University of Seville, Spain.
SOURCE: DIABETES, (2000 Aug) 49 (8) 1288-94.
Journal code: E8X; 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000824
Last Updated on STN: 20000824
Entered Medline: 20000815

AB Pancreastatin (PST), a chromogranin A-derived peptide, has counterregulatory effects on insulin in the hepatocyte and the adipocyte, suggesting a possible role in insulin resistance. The mechanism of PST action on glucose and lipid metabolism is typical of a calcium-mobilizing hormone and involves a receptor Gq/11 protein-phospholipase C (PLC)-beta pathway. In the rat adipocyte, PST inhibits insulin-mediated glucose transport, glucose utilization, and lipid synthesis, and it has a **lipolytic**

effect but stimulates basal and insulin-stimulated protein synthesis. We have also recently studied the PST receptor-effector system in adipocyte membranes. To further investigate the mechanisms of PST effect on insulin action, we studied the cross-talk of PST with insulin signaling in the rat adipocyte. We found that PST inhibits insulin-stimulated GLUT4 translocation to the membrane, which may explain the reported inhibition of glucose transport. Tyrosine phosphorylation of the activated insulin receptor, insulin receptor substrate (IRS)-1, and p60-70 was also blunted, preventing their association with p85 phosphatidylinositol 3-kinase (PI3K) and their activity. The mechanism of this inhibition involves the activation of the "classical" protein kinase C isoforms and the serine phosphorylation of insulin receptor and IRS-1. On the other hand, PST activates the **mitogen-activated** protein **kinase** (**MAPK**) signaling module and enhances the effect of insulin. This pathway may account for the described effect of PST on protein synthesis. In conclusion, PST seems to inhibit the insulin-stimulated PI3K pathway in the adipocyte, whereas it activates the **MAPK** pathway. These data provide some clues to the PST cross-talk with insulin signaling that may explain the PST effects on glucose metabolism and protein synthesis.

L10 ANSWER 5 OF 24 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000164218 MEDLINE
DOCUMENT NUMBER: 20164218 PubMed ID: 10700046
TITLE: Establishment of culture systems of human gastric epithelium for the study of pepsinogen and gastric lipase synthesis and secretion.
AUTHOR: Basque J R; Menard D
CORPORATE SOURCE: MRC Research Group on Functional Development and Physiopathology of the Gastrointestinal Tract, Department of Anatomy and Cell Biology, Faculty of Medicine, Universite de Sherbrooke, Sherbrooke (Quebec) Canada.
SOURCE: MICROSCOPY RESEARCH AND TECHNIQUE, (2000 Mar 1) 48 (5) 293-302. Ref: 57
Journal code: BAG; 9203012. ISSN: 1059-910X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000421
Last Updated on STN: 20000421
Entered Medline: 20000411

Searcher : Shears 308-4994

AB A main purpose of gastric secretion pertains to the digestion of dietary proteins and involves the release of pepsinogens by the fundic and antral mucosa. Over the last decade, data on human gastric physiology has expanded to equally include a significant role in fat digestion. Characteristics of human gastric lipase (HGL) such as optimum acid pH, resistance to proteolysis and non requirement of bile salts or cofactors, are advantageous in gastric **lipolysis**. Furthermore, the importance of HGL increases in the context of perinatal physiology and pathological situations where secretion of HGL could compensate, to some extent the depressed pancreatic activities. It is therefore important to understand the regulatory mechanisms involved in the synthesis and secretion of human gastric digestive enzymes. The establishment of an organ culture technique as well as a novel primary culture system of human gastric epithelium permitted us to demonstrate that Pg5 and HGL are colocalized in human chief cells and both digestive enzymes are efficiently synthesized and secreted in explants and primary cultures. Pepsin activity rises at the cellular level while its secretion remains constant. In contrast, cellular lipase activity drastically diminishes while being preferentially secreted. This nonparallelism supports the concept that Pg5 and HGL are differently regulated in culture. Furthermore, EGF downregulates HGL expression at the mRNA level via the p42/44(**MAPK**) pathway without affecting Pg5. Future studies should be designed to fully understand the cellular and molecular mechanisms involved in regulating HGL activity in normal and pathological conditions.


L10 ANSWER 6 OF 24 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000412215 MEDLINE
DOCUMENT NUMBER: 20314395 PubMed ID: 10854705
TITLE: GH induced **lipolysis** stimulation in 3T3-L1 adipocytes stably expressing hGHR: analysis on signaling pathway and activity of 20K hGH.
AUTHOR: Asada N; Takahashi Y; Wada M; Naito N; Uchida H; Ikeda M; Honjo M
CORPORATE SOURCE: Pharmaceuticals Group, Life Sciences Laboratory, Central Research Institute, Mitsui Chemicals, Inc, Chiba, Japan.
SOURCE: MOLECULAR AND CELLULAR ENDOCRINOLOGY, (2000 Apr 25) 162 (1-2) 121-9.
Journal code: E69; 7500844. ISSN: 0303-7207.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000907

Searcher : Shears 308-4994

Last Updated on STN: 20000907
Entered Medline: 20000828

AB We have constructed a cell line of 3T3-L1 which can efficiently express human GHR (3T3-L1-hGHR) after differentiation to adipocytes. The expressed hGHR was detected as two bands with approximate molecular sizes of 120K by Western analysis using hGHR specific monoclonal antibody. Maximum **lipolytic** activity induced by hGH in the 3T3-L1-hGHR was enhanced 10-fold as compared to that in 3T3-L1, suggesting that expressed hGHR is functionally active. Comparative analysis using bGH and hGH revealed that 70% of **lipolysis** stimulation by 1-10 ng/ml hGH could be attributed to hGHR-mediated response. Analyses on inhibition and phosphorylation of signaling molecules suggested that GH-induced **lipolysis** stimulation is dependent on gene expression and not mediated through PKA-, PKC-, PLA-, PLC-, nor **MAPK** -pathway but possibly through JAK-STATs pathway. Duration of STAT5 activation by hGH continued up to 48 h. We also revealed that 22 K hGH isoform, 20K hGH which has been reported as a weaker agonist for GH-induced **lipolysis** stimulation, possesses equipotent activity and shows stronger action in the presence of hGHBP as compared to 22 K hGH. Taken together we conclude that the hGH-induced **lipolysis** was not mediated through MAP-, PKA-, PKC-, nor PLA-pathway but might be mediated through STAT pathway and that 20K hGH might show higher **lipolytic** activity than 22 K hGH in adipose tissue that produces a large amount of GHBP.

L10 ANSWER 7 OF 24 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000408880 EMBASE
TITLE: Structure, function, and regulation of Group V phospholipase A2.
AUTHOR: Cho W.
CORPORATE SOURCE: W. Cho, Department of Chemistry, M/C 111, University of Illinois, 845 West Taylor Street, Chicago, IL 60607-7061, United States. wcho@uic.edu
SOURCE: Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids, (31 Oct 2000) 1488/1-2 (48-58). Refs: 60
ISSN: 1388-1981 CODEN: BBMLFG
PUBLISHER IDENT.: S 1388-1981(00)00109-8
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The hydrolysis of membrane phospholipid by phospholipase A2 (PLA2) is a key step in the production of inflammatory eicosanoids. Recent cell studies have shown that secretory group V PLA2 (gVPLA2) is involved in agonist-induced eicosanoid biosynthesis in mouse P388D1

cell line, mast cells, and transfected HEK 293 cells. gVPLA2 is homologous to other group II PLA2 family members but has distinctive enzymatic properties, including its activity to effectively hydrolyze phosphatidylcholine (PC) vesicles and the outer plasma membrane of mammalian cells. Mutational studies showed that gVPLA2 has a unique structure that allows effective binding to PC membranes and efficient catalysis of an active-site-bound PC substrate. Thanks to this unique structure and activity, exogenously added gVPLA2 can induce the eicosanoid biosynthesis in unstimulated inflammatory cells, including human neutrophils and eosinophils, suggesting that it might be able to trigger inflammatory responses under certain physiological conditions. Extensive structure-function and cell studies showed that gVPLA2 could act directly on the outer plasma membranes of neutrophils and eosinophils. The release of fatty acids and lysophospholipids from the cell surfaces induces the translocation and activation of cytosolic PLA2 and 5-lipoxygenase, resulting in the leukotriene synthesis. In case of neutrophils, induction of leukotriene B4 synthesis by gVPLA2 leads to the phosphorylation of cytosolic PLA2 by a leukotriene B4 receptor and MAP kinase-mediated mechanism. Finally, heparan sulfate proteoglycans in neutrophils appear to play a role of internalizing and degrading the cell surface-bound gVPLA2 to protect the cells from extensive **lipolytic** damage. (C) 2000 Elsevier Science B.V.

L10 ANSWER 8 OF 24 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-052682 [04] WPIDS
DOC. NO. NON-CPI: N2000-041121
DOC. NO. CPI: C2000-013540
TITLE: Treating or preventing insulin resistance or related disorders.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): GREENBERG, A S
PATENT ASSIGNEE(S): (TUFT) TUFTS COLLEGE
COUNTRY COUNT: 21
PATENT INFORMATION:

Inventor

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9953927 | A1 | 19991028 | (200004)* | EN | 80 |
| RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE | | | | | |
| W: JP US | | | | | |
| EP 1071429 | A1 | 20010131 | (200108) | EN | |
| R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE | | | | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|

| | | | |
|---|---|---|---|
| WO 9953927 | A1 | WO 1999-US8364 | 19990416 |
| EP 1071429 | A1 | EP 1999-917572 | 19990416 |
| | | WO 1999-US8364 | 19990416 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---|---|---|
| EP 1071429 | A1 Based on | WO 9953927 |

PRIORITY APPLN. INFO: US 1998-82741 19980423; US 1998-82152 19980417

AN 2000-052682 [04] WPIDS

AB WO 9953927 A UPAB: 20000124

NOVELTY - A method for preventing or treating a disease or condition caused, or contributed to, by tumor necrosis factor (TNF)- alpha -induced in an individual is new and comprises administering an inhibitor (I) of a **mitogen-activated** protein **kinase** (**MAPK**) pathway to reduce **lipolysis**.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a method for determining whether a subject has or is likely to develop a disease or condition caused, or contributed to, by **lipolysis**, comprising, determining the activity of an EPK1/2 and/or **JNK** in the individual, and wherein an abnormally high **ERK1**/2 and/or **JNK** activity indicates that the individual has or is likely to develop a disease or condition caused, or contributed to, by **lipolysis**; and

(2) a drug screening method for identifying a compound which reduces TNF-A induced **lipolysis** comprising:

(a) isolating a compound which is an **ERK1**/2 and/or **JNK** inhibitor;

(b) contacting an adipocyte with the compound of step (a) and TNF- alpha ; and

(c) determining the level of **lipolysis**, wherein a lower level of **lipolysis** in the presence of the compound of step (a) relative to the level of **lipolysis** in the absence of the compound of step (a) indicates that the compound reduces **lipolysis**.

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - (I) is a direct inhibitor and decreases the protein levels of **ERK1**/2 and/or **JNK** by interacting with their gene and decreasing their expression (claimed).

USE - (I) is used especially for the treatment of non-insulin dependent diabetes mellitus (claimed).

ADVANTAGE - No advantages stated in the specification.
Dwg.0/12

L10 ANSWER 9 OF 24 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999223529 MEDLINE
DOCUMENT NUMBER: 99223529 PubMed ID: 10207024
TITLE: The beta3-adrenergic receptor activates **mitogen-activated** protein **kinase** in adipocytes through a Gi-dependent mechanism.
AUTHOR: Soeder K J; Snedden S K; Cao W; Della Rocca G J; Daniel K W; Luttrell L M; Collins S
CORPORATE SOURCE: Department of Pharmacology, Duke University Medical Center, Durham, North Carolina 27710, USA.
CONTRACT NUMBER: DK02352 (NIDDK)
DK46793 (NIDDK)
DK53092 (NIDDK)
+
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY (1999 Apr 23) 274 (17) 12017-22.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 20000303
Entered Medline: 19990520

AB Promiscuous coupling between G protein-coupled receptors and multiple species of heterotrimeric G proteins provides a potential mechanism for expanding the diversity of G protein-coupled receptor signaling. We have examined the mechanism and functional consequences of dual Gs/Gi protein coupling of the beta3-adrenergic receptor (beta3AR) in 3T3-F442A adipocytes. The beta3AR selective agonist disodium (R, R)-5-[2[[2-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl]-1, 3-benzodioxole-2,2-dicarboxylate (CL316,243) stimulated a dose-dependent increase in cAMP production in adipocyte plasma membrane preparations, and pretreatment of cells with pertussis toxin resulted in a further 2-fold increase in cAMP production by CL316,243. CL316,243 (5 microM) stimulated the incorporation of 8-azido-[32P]GTP into Galphas (1.57 +/- 0.12; n = 3) and Galphai (1. 68 +/- 0.13; n = 4) in adipocyte plasma membranes, directly demonstrating that beta3AR stimulation results in Gi-GTP exchange. The beta3AR-stimulated increase in 8-azido-[32P]GTP labeling of Galphai was equivalent to that obtained with the A1-adenosine receptor agonist N6-cyclopentyladenosine (1.56 +/- 0.07; n = 4), whereas inclusion of unlabeled GTP (100 microM)

eliminated all binding. Stimulation of the beta3AR in 3T3-F442A adipocytes led to a 2-3-fold activation of **mitogen-activated** protein (MAP) **kinase**, as measured by extracellular **signal-regulated kinase** -1 and -2 (**ERK1**/2) phosphorylation. Pretreatment of cells with pertussis toxin (PTX) eliminated MAP kinase activation by beta3AR, demonstrating that this response required receptor coupling to Gi. Expression of the human beta3AR in HEK-293 cells reconstituted the PTX-sensitive stimulation of MAP kinase, demonstrating that this phenomenon is not exclusive to adipocytes or to the rodent beta3AR. **ERK1**/2 activation by the beta3AR was insensitive to the cAMP-dependent protein kinase inhibitor H-89 but was abolished by genistein and AG1478. These data indicate that constitutive beta3AR coupling to Gi proteins serves both to restrain Gs-mediated activation of adenylyl cyclase and to initiate additional signal transduction pathways, including the **ERK1** /2 MAP kinase cascade.

L10 ANSWER 10 OF 24 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000029662 MEDLINE
DOCUMENT NUMBER: 20029662 PubMed ID: 10559135
TITLE: Activation of epithelial growth factor receptor pathway by unsaturated fatty acids.
AUTHOR: Vacaresse N; Lajoie-Mazenc I; Auge N; Suc I; Frisach M F; Salvayre R; Negre-Salvayre A
CORPORATE SOURCE: INSERM U-466 and Department of Biochemistry, IFR-31, CHU Rangueil, Toulouse, France.
SOURCE: CIRCULATION RESEARCH, (1999 Nov 12) 85 (10) 892-9. Journal code: DAJ; 0047103. ISSN: 1524-4571.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20010521
Entered Medline: 19991202

AB Nonesterified fatty acids (NEFAs) are acutely liberated during **lipolysis** and are chronically elevated in pathological conditions, such as insulin resistance, hypertension, and obesity, which are known risk factors for atherosclerosis. The purpose of this study was to investigate the effect and mechanism of action of NEFAs on the epithelial growth factor (EGF) receptor (EGFR). In the ECV-304 endothelial cell line, unsaturated fatty acids triggered a time- and dose-dependent tyrosine phosphorylation of EGFR (polyunsaturated fatty acids [PUFAs] were the most active), whereas saturated FAs were inactive. Although less potent than PUFAs, oleic acid (OA) was used because it is prominent in the South European

diet and is only slightly oxidizable (thus excluding oxidation derivatives). EGFR is activated by OA independent of any autocrine secretion of EGF or other related mediators. OA-induced EGFR autophosphorylation triggered EGFR signaling pathway activation (as assessed through coimmunoprecipitation of SH2 proteins such as SHC, GRB2, and SHP-2) and subsequent p42/p44 **mitogen-activated** protein **kinase** (as shown by the use of EGFR- deficient B82L and EGFR- transduced B82LK(+) cell lines). OA induced in vitro both autophosphorylation and activation of intrinsic tyrosine kinase of immunopurified EGFR, thus suggesting that EGFR is a primary target of OA. EGFR was also activated by mild surfactants, Tween-20 and Triton X-100, both in vitro (on immunopurified EGFR) and in intact living cells, thus indicating that EGFR is sensitive to amphiphilic molecules. These data suggest that EGFR is activated by OA and PUFAs, acts as a sensor for unsaturated fatty acids (and amphiphilic molecules), and is a potential transducer by which diet composition may influence vascular wall biology.

L10 ANSWER 11 OF 24 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 7

ACCESSION NUMBER: 1999118239 EMBASE
TITLE: Epidermal growth factor and transforming growth factor .alpha. down-regulate human gastric lipase gene expression.
AUTHOR: Tremblay E.; Basque J.R.; Rivard N.; Menard D.
CORPORATE SOURCE: Dr. D. Menard, Department of Anatomy/Cell Biology, Faculte de Medecine, Universite de Sherbrooke, Sherbrooke, Que. J1H 5N4, Canada. dmenard@courrier.usherb.ca
SOURCE: Gastroenterology, (1999) 116/4 (831-841). Refs: 54 ISSN: 0016-5085 CODEN: GASTAB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background and Aims: It was recently reported that human gastric lipase (HGL) activity is modulated by epidermal growth factor (EGF). The aims of this study were to establish the cellular localization of HGL, to assess the correlation between HGL messenger RNA (mRNA) and protein levels, and to establish the molecular mechanism of action of EGF and its homologue transforming growth factor .alpha. (TGF-.alpha.) on HGL expression. Methods: Cellular localization of HGL was determined by immunohistochemistry using a polyclonal antibody. Enzymic determinations, Western blotting, and Northern hybridization were used to analyze expression of HGL mRNA, protein,

lipase activity, and the p42/p44(**mapk**) activation status. Results: HGL was localized in the secretory granules of gastric chief cells as early as 13 weeks. A close parallelism was found between the variations of mRNA, protein, and enzymic activity. EGF and/or TGF-.alpha. down-regulated HGL mRNA levels and decreased enzymic activity. The role of the **mitogen-activated** protein **kinase** cascade in the regulation of HGL expression was highlighted by the use of MAP kinase kinase-1/2 inhibitor PD98059, which blunted both the activation of p42/p44(**mapk**) and the down-regulation of HGL mRNA induced by EGF and/or TGF- .alpha.. Conclusions: The expression of HGL is regulated at the mRNA level, and the down-regulatory action of EGF and/or TGF-.alpha. on HGL involves the stimulation of p42/p44(**mapk**) cascade.

L10 ANSWER 12 OF 24 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 1999:140377 SCISEARCH
THE GENUINE ARTICLE: 165JQ
TITLE: Stimulation of the extracellular **signal-regulated kinase** 1/2 pathway by human beta-3 adrenergic receptor: New pharmacological profile and mechanism of activation
AUTHOR: Gerhardt C C; Gros J; Strosberg A D; Issad T (Reprint)
CORPORATE SOURCE: INST COCHIN GENET MOL, CNRS, UNITE PROPRE RECH 415, LAB IMMUNOPHARMACOL MOL, 22 RUE MECHAIN, F-75014 PARIS, FRANCE (Reprint); INST COCHIN GENET MOL, CNRS, UNITE PROPRE RECH 415, LAB IMMUNOPHARMACOL MOL, F-75014 PARIS, FRANCE; UNIV PARIS 07, LAB IMMUNOPHARMACOL MOL, F-75014 PARIS, FRANCE
COUNTRY OF AUTHOR: FRANCE
SOURCE: MOLECULAR PHARMACOLOGY, (FEB 1999) Vol. 55, No. 2, pp. 255-262.
Publisher: AMER SOC PHARMACOLOGY EXPERIMENTAL THERAPEUTICS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998.
ISSN: 0026-895X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 37

*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB We present evidence that stimulation of the human beta-3 adrenergic receptor (AR), expressed in Chinese hamster ovary/K1 cells, specifically activates the **mitogen-activated** protein **kinases** extracellular **signal-regulated kinase** (**ERK**)1 and 2, but not **JNK** or p38. The extent and kinetics of the

**ERK** stimulation by the beta-3 AR are identical with those of the endogenic insulin receptor. However, insulin augments cellular proliferation, whereas beta-3 AR agonists inhibit proliferation due to the production of cyclic AMP. The pharmacological profile of the **ERK** activation by the beta-3 AR differs significantly from its activation of adenylyl cyclase. The order of potency and intrinsic activities of both natural ligands, norepinephrine and epinephrine, is inversed between both signaling pathways. In addition, BRL 37344 and propranolol, ligands that act as agonists in the stimulation of cyclase, act as antagonists for **ERK** activation. The activation of **ERK1/2** is sensitive to pertussis toxin, suggesting that the beta-3 AR, in addition to its interaction with G(s), can couple to G(i/o). Furthermore, the activation of **ERK** by the beta-3 AR is sensitive to PD98059, wortmannin, and LY294002, indicating a crucial role for **mitogen-activated** protein **kinase** **kinase** and phosphatidylinositol-3 kinase (PI3K), respectively. A beta-3 AR-mediated stimulation of PI3K is confirmed by the observation that the selective agonist CGP 12177A specifically activates protein kinase B. As was observed for the activation of **ERK**, the activation of protein kinase B is inhibited by preincubation with pertussis toxin and PI3K inhibitors, suggesting that both are a consequence of a G(i/o)-mediated activation of PI3K.

L10 ANSWER 13 OF 24 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999333510 EMBASE
TITLE: [Metabolic and trophic role of catecholamines in the development of white adipose tissue].
ROLE METABOLIQUE ET TROPHIQUE DES CATECHOLAMINES SUR LE DEVELOPPEMENT DU TISSU ADIPEUX BLANC.
AUTHOR: Valet P.; Saulnier-Blache J.S.
CORPORATE SOURCE: P. Valet, INSERM U317, CHU Rangueil, Universite Paul-Sabatier, 31403 Toulouse Cedex 4, France
SOURCE: Annales d'Endocrinologie, (1999) 60/3 (167-174).
Refs: 31
ISSN: 0003-4266 CODEN: ANENAG
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
LANGUAGE: French
SUMMARY LANGUAGE: English; French
AB The fat cell is of key significance to the physiologist investigating the mechanisms controlling lipid storage, mobilization and utilization as well as other functions of the adipose tissue. Insulin and catecholamines are the major hormonal regulators of **lipolysis**. Four adrenoceptor subtypes are involved in the adrenergic regulation of fat cell **lipolysis**. The control

of adenylyl cyclase activity involves stimulatory .beta.1-, .beta.2- and .beta.3-adrenergic receptors and inhibitory .alpha.2-adrenergic receptors. Their control of **lipolysis** is subjected to variations according to the anatomical localization of adipose tissue deposits. In humans, **lipolysis** differs in visceral and subcutaneous deposits. Changes in .beta.- and .alpha.2-adrenoceptor ratios and function have been proposed to explain the **lipolytic** disturbances. Human and rodent white adipocytes differ dramatically with respect to the balance between and b-adrenergic receptors. Human adipocytes express mainly .alpha.2 and few b3-adrenergic receptors while the reverse is true for rodent adipocytes. Preadipocyte .alpha.2-adrenergic receptor stimulation initiates proliferation mediated by MAPkinase activation and cytoskeleton re-arrangements. We have generated transgenic mice on a b3-adrenergic receptor gene knock-out background which express human .alpha.2-adrenergic receptors selectively in white and brown fat cells by using an adipocyte-specific prorooter. No phenotype was noticed in the mice fed with a standard diet, by contrast a large increase in body weight was observed when the animals are fed with a high fat diet. The weight gain concerns fat deposits and is mainly characterized by a large increase in fat cell number. This phenotype is due to an interaction between two genes and the diet since the unique combination of a high fat diet, absence of b3-adrenergic receptors and presence of .alpha.2-adrenergic receptors promotes hyperplastic development of fat deposits and increased weight gain.

L10 ANSWER 14 OF 24 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2000062699 MEDLINE
DOCUMENT NUMBER: 20062699 PubMed ID: 10594345
TITLE: Phosphorylation of extracellular **signal-regulated kinases** 1 and 2 in 3T3-L1 adipocytes by stimulation of beta(3)-adrenoceptor.
AUTHOR: Mizuno K; Kanda Y; Kuroki Y; Tomiyama K; Watanabe Y
CORPORATE SOURCE: Department of Pharmacology, National Defense Medical College, 3-2 Namiki, Tokorozawa, Japan.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1999 Nov 26) 385 (1) 63-9.
Journal code: EN6; 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000214
AB Recent studies have revealed that activated extracellular **signal-regulated kinases** (**ERKs**

) 1 and 2 by the stimulation of beta(3)-adrenoceptors played a critical role in cell survival in brown adipocytes. On the other hand, phosphorylation of **ERK1**/2 via beta(3)-adrenoceptors and its physiological and pathological significance in white adipocyte has remained uncertain despite the increasing significance of functioning white adipocytes. Accordingly, we here studied phosphorylation of **ERK1**/2 caused by the stimulation of beta(3)-adrenoceptors in 3T3-L1 adipocytes, and the roles of phosphorylated **ERK1**/2 in **lipolysis**.
Phosphorylation of **ERK1**/2 was induced by a selective beta(3)-adrenoceptor agonist, DL-4-[2'- 2-hydroxy-2-(3-chlorophenyl)ethylamino propyl] phenoxyacetic acid sodium salt sesquihydrate (BRL37344), in 3T3-L1 adipocytes in a time- and dose-dependent manner. The phosphorylation of **ERK1**/2 by BRL37344 was sensitive to the cyclic AMP (cAMP)-dependent protein kinase inhibitor, N-[2-((p-bromocinnamyl)amino)ethyl]-5-isoquinolinesulfonamide (H89). To elucidate the roles of phosphorylated **ERK1**/2 in **lipolysis**, the effect of a selective inhibitor of **ERK1**/2 phosphorylation, 2'-amino-3'-methoxyflavone (PD98059), was examined. This inhibitor did not alter the **lipolytic** action caused by BRL37344, even at concentrations sufficient to block phosphorylation of **ERK1**/2, suggesting that **ERK1**/2 play no role in the **lipolysis** caused by BRL37344 in 3T3-L1 adipocytes.

L10 ANSWER 15 OF 24 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 1998288315 MEDLINE
DOCUMENT NUMBER: 98288315 PubMed ID: 9624169
TITLE: Growth hormone and prolactin stimulate tyrosine phosphorylation of insulin receptor substrate-1, -2, and -3, their association with p85 phosphatidylinositol 3-kinase (PI3-kinase), and concomitantly PI3-kinase activation via JAK2 kinase.
AUTHOR: Yamauchi T; Kaburagi Y; Ueki K; Tsuji Y; Stark G R; Kerr I M; Tsushima T; Akanuma Y; Komuro I; Tobe K; Yazaki Y; Kadowaki T
CORPORATE SOURCE: Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo 113, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Jun 19) 273 (25) 15719-26.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980716
Last Updated on STN: 20000303

Searcher : Shears 308-4994

Entered Medline: 19980709

AB Growth hormone (GH) and prolactin (PRL) binding to their receptors, which belong to the cytokine receptor superfamily, activate Janus kinase (JAK) 2 tyrosine kinase, thereby leading to their biological actions. We recently showed that GH mainly stimulated tyrosine phosphorylation of epidermal growth factor receptor and its association with Grb2, and concomitantly stimulated **mitogen -activated** protein **kinase** activity in liver, a major target tissue. Using specific antibodies, we now show that GH was also able to induce tyrosine phosphorylation of insulin receptor substrate (IRS)-1/IRS-2 in liver. In addition, the major tyrosine-phosphorylated protein in anti-p85 phosphatidylinositol 3-kinase (PI3-kinase) immunoprecipitate from liver of wild-type mice was IRS-1, and IRS-2 in IRS-1 deficient mice, but not epidermal growth factor receptor. These data suggest that tyrosine phosphorylation of IRS-1 may be a major mechanism for GH-induced PI3-kinase activation in physiological target organ of GH, liver. We also show that PRL was able to induce tyrosine phosphorylation of both IRS-1 and IRS-2 in COS cells transiently transfected with PRLR and in CHO-PRLR cells. Moreover, we show that tyrosine phosphorylation of IRS-3 was induced by both GH and PRL in COS cells transiently transfected with IRS-3 and their cognate receptors. By using the JAK2-deficient cell lines or by expressing a dominant negative JAK2 mutant, we show that JAK2 is required for the GH- and PRL-dependent tyrosine phosphorylation of IRS-1, -2, and -3. Finally, a specific PI3-kinase inhibitor, wortmannin, completely blocked the anti-**lipolytic** effect of GH in 3T3 L1 adipocytes. Taken together, the role of IRS-1, -2, and -3 in GH and PRL signalings appears to be phosphorylated by JAK2, thereby providing docking sites for p85 PI3-kinase and activating PI3-kinase and its downstream biological effects.

L10 ANSWER 16 OF 24 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1998256309 MEDLINE
DOCUMENT NUMBER: 98256309 PubMed ID: 9593725
TITLE: Association of the insulin receptor with phospholipase C-gamma (PLCgamma) in 3T3-L1 adipocytes suggests a role for PLCgamma in metabolic signaling by insulin.
AUTHOR: Kayali A G; Eichhorn J; Haruta T; Morris A J; Nelson J G; Vollenweider P; Olefsky J M; Webster N J
CORPORATE SOURCE: UCSD/Whittier Diabetes Program, University of California San Diego, La Jolla, California 92093 and the Medical Research Service, Department of Veterans Affairs, Medical Center, San Diego, California 92161, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 May 29) 273 (22) 13808-18.

Searcher : Shears 308-4994

Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980713
Last Updated on STN: 20000303
Entered Medline: 19980701

AB Phospholipase C-gamma (PLCgamma) is the isozyme of PLC phosphorylated by multiple tyrosine kinases including epidermal growth factor, platelet-derived growth factor, nerve growth factor receptors, and nonreceptor tyrosine kinases. In this paper, we present evidence for the association of the insulin receptor (IR) with PLCgamma. Precipitation of the IR with glutathione S-transferase fusion proteins derived from PLCgamma and coimmunoprecipitation of the IR and PLCgamma were observed in 3T3-L1 adipocytes. To determine the functional significance of the interaction of PLCgamma and the IR, we used a specific inhibitor of PLC, U73122, or microinjection of SH2 domain glutathione S-transferase fusion proteins derived from PLCgamma to block insulin-stimulated GLUT4 translocation. We demonstrate inhibition of 2-deoxyglucose uptake in isolated primary rat adipocytes and 3T3-L1 adipocytes pretreated with U73122. Antilipolytic effect of insulin in 3T3-L1 adipocytes is unaffected by U73122. U73122 selectively inhibits **mitogen-activated** protein **kinase**, leaving the Akt and p70 S6 kinase pathways unperturbed. We conclude that PLCgamma is an active participant in metabolic and perhaps mitogenic signaling by the insulin receptor in 3T3-L1 adipocytes.

L10 ANSWER 17 OF 24 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 1998:462702 SCISEARCH
THE GENUINE ARTICLE: ZL335
TITLE: TNF-alpha increases **lipolysis** through activation of **ERK** and JNK1 MAP kinase pathways in 3T3-L1 adipocytes
AUTHOR: Souza S C (Reprint); Palmer H J; Lien P; Paulson K E; Greenberg A S
SOURCE: DIABETES, (MAY 1998) Vol. 47, Supp. [1], pp. 1308-1308.
Publisher: AMER DIABETES ASSOC, 1660 DUKE ST, ALEXANDRIA, VA 22314.
ISSN: 0012-1797.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L10 ANSWER 18 OF 24 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 1998:918689 SCISEARCH
THE GENUINE ARTICLE: 143CW
TITLE: The activation of p38 **MAPK** by the beta-adrenergic agonist isoproterenol in rat epididymal fat cells
AUTHOR: Moule S K (Reprint); Denton R M
CORPORATE SOURCE: SCH MED SCI, DEPT BIOCHEM, UNIV WALK, BRISTOL BS8 1TD, AVON, ENGLAND (Reprint)
COUNTRY OF AUTHOR: ENGLAND
SOURCE: FEBS LETTERS, (20 NOV 1998) Vol. 439, No. 3, pp. 287-290.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0014-5793.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 33

*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Here we report that the beta-adrenergic agonist isoproterenol increases the activity of the stress-activated kinase p38 **MAPK** over 10-fold in freshly isolated rat epididymal fat cells. Stimulation of the kinase was rapid, sustained for at least 60 min and sensitive to the specific p38 **MAPK** inhibitor, SE 203580, Half-maximal stimulation of p38 **MAPK** by isoproterenol occurred at 13 nM isoproterenol. The cell permeable cyclic AMP analogue, chlorophenylthio-cyclic AMP increased p38 **MAPK** activity to a similar er;tent to isoproterenol, suggesting that the effect of the beta-adrenergic agonist is mediated via increases in the activity of cyclic-AMP dependent protein kinase, Although it had little or no effect on the activity of c-**Jun** N-terminal **kinase**, isoproterenol and a number of other treatments which activated p38 **MAPK** were found to stimulate AR;activated protein kinase in fat cells, Activation of AMPK and p38 **MAPK** were not, however, found to be directly linked. (C) 1998 Federation of European Biochemical Societies.

L10 ANSWER 19 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 11
ACCESSION NUMBER: 1998:72028 BIOSIS
DOCUMENT NUMBER: PREV199800072028
TITLE: Insulin-induced phosphorylation and activation of phosphodiesterase 3B in rat adipocytes: Possible role for protein **kinase** B but not **mitogen-activated** protein **kinase** or p70 S6 **kinase**.

Searcher : Shears 308-4994

AUTHOR(S): Wijkander, Jonny; Landstrom, Tova Rahn; Manganiello, Vincent; Belfrage, Per; Degerman, Eva (1)
CORPORATE SOURCE: (1) Sect. Mol. Signaling, Dep. Cell Mol. Biol., Univ. Lund, P.O. Box 94, S-221 00 Lund Sweden
SOURCE: Endocrinology, (Jan., 1998) Vol. 139, No. 1, pp. 219-227.
ISSN: 0013-7227.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Insulin stimulation of adipocytes results in serine phosphorylation/activation of phosphodiesterase 3B (PDE 3B) and activation of a kinase that phosphorylates PDE 3B in vitro, key events in the anti-**lipolytic** action of this hormone. We have investigated the role for p70 S6 **kinase**, **mitogen-activated** protein **kinases** (MAP **kinases**), and protein kinase B (PKB) in the insulin signaling pathway leading to phosphorylation/activation of PDE 3B in adipocytes. Insulin stimulation of adipocytes resulted in increased activity of p70 S6 kinase, which was completely blocked by pretreatment with rapamycin. However, rapamycin had no effect on the insulin-induced phosphorylation/activation of PDE 3B or the activation of the kinase that phosphorylates PDE 3B. Stimulation of adipocytes with insulin or phorbol myristate acetate induced activation of MAP kinases. Pretreatment of adipocytes with the MAP kinase kinase inhibitor PD 98059 was without effect on the insulin-induced activation of PDE 3B. Furthermore, phorbol myristate acetate stimulation did not result in phosphorylation/activation of PDE 3B or activation of the kinase that phosphorylates PDE 3B. Using Mono Q and Superdex chromatography, the kinase that phosphorylates PDE 3B was found to co-elute with PKB, but not with p70 S6 kinase or MAP kinases. Furthermore, both PKB and the kinase that phosphorylates PDE 3B were found to translocate to membranes in response to peroxovanadate stimulation of adipocytes in a wortmannin-sensitive way. Whereas these results suggest that p70 S6 kinase and MAP kinases are not involved in the insulin-induced phosphorylation/activation of PDE 3B in rat adipocytes, they are consistent with PKB being the kinase that phosphorylates PDE 3B.

L10 ANSWER 20 OF 24 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 1998222618 MEDLINE
DOCUMENT NUMBER: 98222618 PubMed ID: 9561805
TITLE: **Mitogen-activated** protein **kinase** and p70 ribosomal protein S6 kinase are not involved in the insulin-dependent stimulation of cAMP phosphodiesterase kinase in rat adipocytes.
AUTHOR: Onuma H; Makino H; Osawa H; Suzuki Y; Taira M; Kanatsuka A; Saito Y

Searcher : Shears 308-4994

CORPORATE SOURCE: Department of Laboratory Medicine, Ehime University School of Medicine, Japan.
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (1998 Mar 27) 1402 (2) 197-208.
Journal code: A0W; 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980529
Last Updated on STN: 20000303
Entered Medline: 19980521

AB To elucidate the mechanism of anti-**lipolytic** action of insulin in rat epididymal adipocytes, we explored the potential mechanism that might be involved in the hormone-dependent stimulation of cAMP phosphodiesterase (PDE) kinase. PDE kinase was assayed in a cell-free system. Both wortmannin and LY294002, highly specific inhibitors of phosphatidylinositol 3-kinase, almost completely blocked the hormonal effect not only on PDE **kinase** but also on **mitogen-activated** protein (MAP) **kinase**. Neither PD98059, a specific inhibitor of MAP kinase, nor rapamycin, a potent inhibitor of insulin-dependent stimulation of p70 ribosomal protein S6 kinase (p70S6K), had inhibitory effect on that of PDE kinase. These results are consistent with the view that (i) insulin-activated PDE kinase as well as MAP kinase and p70S6K are localized downstream of phosphatidylinositol 3-kinase, (ii) PDE kinase is distinct from either MAP kinase or p70S6K and (iii) PDE kinase does not exist downstream of either MAP kinase or p70S6K. It is suggested that PDE kinase and MAP kinase or p70S6K may be localized in separate branches of the cascade of insulin action. The branching point of the cascade could be either at or below the level of phosphatidylinositol 3-kinase.

L10 ANSWER 21 OF 24 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 97350860 MEDLINE
DOCUMENT NUMBER: 97350860 PubMed ID: 9207236
TITLE: Functional consequences of constitutively active alpha2A-adrenergic receptor expression in 3T3F442A preadipocytes and adipocytes.
AUTHOR: Betuing S; Valet P; Lapalu S; Peyroulan D; Hickson G; Daviaud D; Lafontan M; Saulnier-Blache J S
CORPORATE SOURCE: I.N.S.E.R.M U317, Institut Federatif de Recherches Louis Bugnard, Universite Paul Sabatier, CHU Rangueil, Toulouse, France.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1997 Jun 27) 235 (3) 765-73.

Journal code: 9Y8; 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970805
Last Updated on STN: 20000303
Entered Medline: 19970724

AB The functional consequences of a constitutively active mutated (CAM) human alpha2C10-adrenergic receptor (AR) stably expressed in the 3T3F442A preadipose cell line were analysed at both preadipocyte and adipocyte stages. At the preadipocyte stage, CAMalpha2C10-AR reproduced (in the absence of agonist) and amplified (in the presence of agonist) most of the cellular responses promoted by agonist-stimulated wild type alpha2C10-AR (increased preadipocyte proliferation, tyrosyl-phosphorylation of the **Mitogen Activated** Protein **Kinases**, resistance to serum-deprivation-induced cell retraction, inhibition of differentiation). In contrast, at the adipocyte stage, CAMalpha2C10-AR expression did not reproduced nor amplified the alpha2-adrenergic-dependent antilipolysis, but conversely led to a down-regulation of alpha i subunits of the Gi proteins and to an increase in the maximal response to **lipolytic** agents. Our results indicate that long term activation of intracellular signals by CAM-receptors not only lead to the expected cellular responses normally generated by agonist-stimulated wild type receptors, but can also lead to unexpected responses resulting from long term compensatory adaptations.

L10 ANSWER 22 OF 24 MEDLINE DUPLICATE 14

ACCESSION NUMBER: 1998022035 MEDLINE
DOCUMENT NUMBER: 98022035 PubMed ID: 9379129
TITLE: Selective modification of insulin action in adipose tissue by hyperthyroidism.
AUTHOR: Fryer L G; Holness M J; Sugden M C
CORPORATE SOURCE: Department of Biochemistry, Basic Medical Sciences, St Bartholomew's London, UK.
SOURCE: JOURNAL OF ENDOCRINOLOGY, (1997 Sep) 154 (3) 513-22.
Journal code: I1J; 0375363. ISSN: 0022-0795.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19990129
Entered Medline: 19971110

AB Adipose-tissue **lipolysis** (assessed from glycerol release) and glucose uptake were examined in parametrial and mesenteric adipocytes prepared from control or hyperthyroid rats in relation to changes in insulin sensitivity. Basal rates of **lipolysis** did not differ significantly between adipose-tissue depots. **Lipolysis** was maximally stimulated by noradrenaline at 1 microM, half-maximal anti-**lipolytic** effects of insulin were observed at approximately 11 microU/ ml insulin, and half-maximal stimulation of glucose uptake was observed at approximately 16 microU/ml insulin in adipocytes from both depots. Wortmannin caused a dose-dependent inhibition of the anti-**lipolytic** effect of insulin (150 microU/ml) on noradrenaline-stimulated **lipolysis**. Half-maximal effects of wortmannin were observed at 20-40 nM. The p70S6K inhibitor rapamycin and the **mitogen-activated** protein **kinase kinase** inhibitor PD098059 had no effects on noradrenaline-stimulated **lipolysis**. Hyperthyroidism increased basal rates of **lipolysis** and the maximal response of **lipolysis** to noradrenaline stimulation (3.1-fold, $P < 0.001$ and 2.1-fold, $P < 0.05$ respectively) in parametrial adipocytes. Hyperthyroidism markedly blunted the sensitivity of noradrenaline-stimulated **lipolysis** to half-maximal suppression by insulin in both parametrial and mesenteric adipocyte depots, and noradrenaline-stimulated **lipolysis** at a maximal insulin concentration remained significantly higher in adipocytes prepared from hyperthyroid rats compared with controls. Hyperthyroidism had no effect on basal and little effect on insulin-stimulated glucose uptake. Tri-iodothyronine administered at a low dose selectively influenced the anti-**lipolytic** action of insulin in parametrial adipocytes, and led to significantly less marked elevation in plasma non-esterified fatty acid concentrations in vivo. The results demonstrate a selective effect of hyperthyroidism to impair insulin's anti-**lipolytic** action, and are consistent with the operation of different downstream signalling mechanisms for the effects of insulin on adipocyte glucose transport and **lipolysis**.

L10 ANSWER 23 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:452024 BIOSIS
DOCUMENT NUMBER: PREV199799751227
TITLE: Multiple signaling pathways involved in the metabolic effects of insulin.
AUTHOR(S): Moule, S. Kelly; Denton, Richard M. (1)
CORPORATE SOURCE: (1) Dep. Biochemistry, Univ. Bristol Sch. Med. Sci., University Walk, Bristol BS8 1TD UK
SOURCE: American Journal of Cardiology, (1997) Vol. 80, No. SUPPL. 3A, pp. 41A-49A.